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DISEASES OF CHILDREN

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Manley B. Shaw, Kayo Sunada, and Ione A. Hopkey

The Natural History of Mental Deficiency in a State Hospital
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Recurrent Pannicular Hemorrhages
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Congenital Atresia of the Inferior Vena Cava, Common Iliac Veins, and Left Innominate Vein
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TABLE OF CONTENTS

VOLUME 96 JULY 1958 NUMBER 1

ORIGINAL ARTICLES

PAGE

Meningitis Caused by an Unclassified Gram-Negative Bacterium in Newborn Infants
Jacob A. Brody, M.D.; Helen Moore, M.D., and Elizabeth O. King, M.S., Atlanta 1

Long-Term Study of One Hundred Five Patients with Cystic Fibrosis
Harry Shwachman, M.D., and Lucas L. Kulczycki, M.D., Boston 6

The Effect of Graded Doses of Vitamin D on the Serum Calcium and Phosphorus Levels
J. B. Pincus, M.D.; I. F. Gittleman, M.D.; N. Marius, M.S., and B. Bachra, Ph.D., Brooklyn 16

Abnormal Amino Acid Metabolism in a Case Suggesting Autism
H. Eldon Sutton, Ph.D., and John H. Read, M.D., Ann Arbor, Mich. ... 23

Anal Fissures in Infants and Children
Richard M. Alexander, M.D., Great Neck, N. Y., and Sylvan D. Manheim, M.D., New York 29

The Relationship of Little's Disease to Premature Birth
John Alvord Churchill, M.D., Detroit 32

The Determination of Genetic Sex in Children
Kenneth H. Cooper, M.D., Oklahoma City, and Robert L. Cranny, M.D., Salt Lake City 40

Primary Interstitial Myocarditis
Emil Freundlich, M.D.; Maximilian Berkowitz, M.D.; Arie Elkon, M.D., and Abraham Wilder, M.D., Haifa, Israel 43

Sickle-Cell Anemia in Infancy
Sanford L. Leikin, M.D., and James W. McCoo Jr., B.S., Washington, D. C. 51

Clinical Study of Four Hundred Twenty-Five Idaho Poliomyelitis Vaccine Recipients in 1955
Manley B. Shaw, M.D.; Kayo Sunada, M.D., and Ione A. Hopkey, R.N., Boise, Idaho 58

The Natural History of Mental Deficiency in a State Hospital
George Tarjan, M.D.; Stanley W. Wright, M.D.; Morton Kramer, Sc.D.; Philip H. Person Jr., M.S., and Richard Morgan, B.A., Pomona, Calif. 64

CASE REPORTS

Recurrent Pannicular Hemorrhages
Meinhard Robinow, M.D., and William A. Newton Jr., M.D., Yellow Springs, Ohio 71

Congenital Atresia of the Inferior Vena Cava, Common Iliac Veins, and Left Innominate Vein
Kenneth F. Swaiman, M.D.; Sol Austrian, M.D., and Richard B. Raile, M.D., Minneapolis, Minn. 81

REGULAR DEPARTMENTS

Abstracts from Current Literature 87
News and Comment 106
Books 111
Directory of Pediatric Societies 113

A. M. A.
Journal of Diseases of Children

VOLUME 96 JULY 1958 NUMBER 1

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* Fries, J. H., Milk Allergy-Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., Nov. 23, 1957.

** Ibid.

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1947 *Adding strained meat to the formula* of bottle-fed infants checked the characteristic early decrease in hemoglobin level, and promoted the formation of hemoglobin and erythrocytes. (1)

1951 *Strained meats* were found to be an excellent and readily available source of iron for premature infants. (2)

1952 At 20 weeks of age the hemoglobin concentration of meat-fed infants averaged 1.0 gram higher than the control group. More than adequate amounts of iron were added to the diet of both groups. (3)

1952 *Hemoglobin and red cell values* of meat-fed infants rose above those of the control group during a four month period, and dropped when meat supplementation was discontinued. (4)

1952 *Hemoglobin levels* rose in infants first fed meat prior to two months of age. (5)

Final Report on the Hemopoietic Effect of Early Meat Feeding(6)

PURPOSE OF STUDY:

a. To determine if meat would be an effective source of iron in the diet of premature infants.

b & c. To assess the influence of meat supplementation on the circulating hemoglobin mass, total red blood cell volume and serum iron levels over the first year of life.

RESULTS:

a. Red Cell Volume:

At first the controls demonstrated a marked rapid fall of red cell volume, then a continued, though slower, decline. In general, the level reached at 6 weeks of age was maintained only by the administration of medical iron.

In the meat-fed group, as would be expected, the same initial effect was experienced. In general, there was a temporary increase in red cell volume in this group at eight weeks. Subsequent reduction was small.

Between the 16th and 30th weeks the values of the meat-fed infants were generally higher than those of the controls.

Between 28 and 30 weeks of age the red cell volumes of the test group tended to increase.

By the end of the year these values were significantly higher than those of the controls.

b. Total Circulating Hemoglobin Mass

Initially a reduction of hemoglobin was found in both the control and the meat-fed infants.

Between the 6th and 8th weeks this downward trend was reversed in the meat-fed infants, although it was not in the control subjects.

From the 28th to the 30th week the mass was generally well maintained by the test group. From that point on there was an increase in hemoglobin mass in the meat-fed group that was not duplicated in the control group.

c. Serum Iron Levels

Throughout the first year of life, with but two exceptions, the serum iron levels of the control group fell.

Until the 16th week the serum iron levels of the meat-fed group also decreased, then levelled off or rose only slightly until about the 30th week.

After that point the meat-fed group experienced a distinct increase.

CONCLUSION:

The addition of meat to the infant diet supplied a pool of iron for subsequent hemoglobin synthesis, and an increase of iron stores occurred in the infants given this supplement.

The expansion of red cell volume and circulating hemoglobin mass in the meat-fed group was greater than in the controls.

The steady decline of these values in the control group demonstrates the need for some effective iron source in the diet of the premature infant.

Meat provides an excellent source of protein for the infant diet; and, in this study, is shown to be an acceptable and utilizable form of iron in natural form.

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DISEASES OF CHILDREN

Meningitis Caused by an Unclassified Gram-Negative Bacterium in Newborn Infants

JACOB A. BRODY, M.D.; HELEN MOORE, M.D., and ELIZABETH O. KING, M.S., Atlanta

Bacterial meningitis has not been reported as a frequent cause of death in premature or full-term newborn infants.[1-4] The cases which do occur have not appeared in epidemic form and have been caused in the majority of instances by one of the coliform groups of bacteria. It is of some interest, therefore, that within the past year two outbreaks of a lethal form of meningitis have occurred in hospital nurseries, involving primarily premature infants. The causative agent has not yet been completely defined, but a Gram-negative bacillus was recovered from the spinal fluid of 17 of the 19 victims.

Between June, 1956, and July, 1957, twelve cases occurred in Greenville, S. C., with eight deaths, three surviving hydrocephalics, and only one complete recovery. In Portsmouth, Va., seven cases of meningitis appeared in nursery populations from October, 1956, to October, 1957, all of whom died. Three cultures from Portsmouth and four from Greenville were studied by the Diagnostic Bacteriology Unit of the Communicable Disease Center (CDC) and were found to be identical in colonial, morphological, and biochemical properties. In spite of considerable effort, this organism has not yet been classified. The suggestion that these outbreaks not only are related but that they are part of a more general problem arises from the fact that the same bacterium has been received for identification by CDC from five other states since 1949. This preliminary report summarizes the information that has been collected to date regarding this newly recognized problem.

Submitted for publication Jan. 22, 1958.

From the Communicable Disease Center, Bureau of State Services, Public Health Service, Department of Health, Education, and Welfare. Epidemic Intelligence Service Officer, Surveillance Section, Epidemiology Branch, CDC (Dr. Brody); formerly Epidemiologist, Surveillance Section, CDC; present address: U. S. O. M., La Paz, Bolivia (Dr. Moore); Bacteriologist, Diagnostic Bacteriology Unit, CDC, Chamblee, Ga. (Miss King).

The Greenville Experience

A request for epidemic aid was received by CDC in October, 1956, from the South Carolina State Department of Health, following a series of cases of meningitis in a nursery in Greenville, S. C. One of the authors (H. M.) proceeded to Greenville, and with the cooperation of the hospital staff a study was made of the situation in the nursery and of the records for the previous months. The investigation disclosed that between June 26 and Oct. 6 seven cases of meningitis had occurred among newborn babies weighing less than 2500 gm. Six of the cases had been confined to the nursery for premature infants, where the annual census is about 250. The only child of the group alive during the inquiry had progressive hydrocephalus and subsequently died, while death had occurred in the others in 1 to 17 days from onset of symptoms (Cases 1 to 7, Table 1).

TABLE 1.—*Greenville, S. C., Cases of Meningitis Associated with an Unclassified Gram-Negative Bacillus* *

Case	Weight, Gm.	Birth Date	Day of Onset After Birth	Day of Death After Onset	Bacteriology †	Cerebrospinal Fluid	Remarks
1	2,041	6/26/56	2	5	Blood, Gram-neg. rod	0	No autopsy
2	2,070	8/15/56	8	1	CSF, Gram-neg. rod Blood, Gram-neg. rod	RBC, 1,300; WBC, 810; sugar, 5.5 mg. %	Autopsy, purulent meningitis
3	1,304	8/31/56	9	74	0	0	Hydrocephalus, autopsy, chronic meningitis
4	1,559	8/7/56	17	13	CSF, Gram-neg. rod	Purulent	Autopsy, purulent meningitis
5	2,410	9/18/56	5	2	CSF, Gram-neg. rod Blood, Gram-neg. rod	Bloody tap	Autopsy, purulent meningitis
6	1,616	9/22/56	8	8	CSF, Gram-neg. rod Blood, Gram-neg. rod	WBC, 930; Pandy, 4+	Autopsy, purulent meningitis
7	2,410	10/6/56	8	1	CSF, Gram-neg. rod	WBC, 2,040	No autopsy
8	2,495	10/13/56	7	Alive	Blood, Gram-neg. rod ‡	0	Recovered, no CNS envolvement
9	1,871	2/2/57	9	Alive	CSF, Gram-neg. rod ‡	Clotted, purulent	Marked hydrocephalus
10	946	6/10/57	6	Alive	CSF, no growth, performed on 43d day of life	RBC, 70; WBC, 369; sugar, 16.5 mg. %; protein, 379 mg. %	Hydrocephalus
11	1,219	7/5/57	5	147	CSF, Gram-neg. rod ‡ Throat, Gram-neg. rod ‡	RBC, 340; WBC, 7,800; pandy, 4+	Hydrocephalus; autopsy, chronic meningitis
12	1,304	7/5/57	13	Alive	CSF, Gram-neg. rod ‡	RBC, 3,232; WBC, 10,285	Hydrocephalus

* Case 8 never developed meningitis, but the organism was recovered from her blood.
† Negative and positive blood and cerebrospinal fluid cultures are listed.
‡ Culture identified by the Diagnostic Bacteriology Unit, CDC, as the unclassified organism.

A Gram-negative organism whose etiology was obscure had been recovered from blood or cerebrospinal fluid in six instances. Unfortunately, the cultures had not been preserved. While the situation was still under study, blood for culture was secured from a premature infant having moderate respiratory distress. A Gram-negative bacillus grew out, and when the culture was reviewed by the Diagnostic Bacteriology Unit of the Communicable Disease Center the growth was found to be the unclassified organism referred to previously. This infant recovered without sequellae (Case 8, Table 1). Although this obscure organism had been associated with meningitis on several occasions in the past, its relation to the other cases at Greenville was far from clear.

Close contact was maintained with the hospital, and during the next nine months four more cases of meningitis among premature infants occurred. From three of the babies the same unclassified Gram-negative organism was isolated from the cerebrospinal fluid, and on one occasion, from the throat. With increased awareness of the problem, these children were treated early and vigorously with large doses of chloramphenicol and erythromycin or oleandomycin. Whether this influenced the clinical course is not certain, but all of this latter group survived the acute phase, developing progressive hydrocephalus, to which one has already succumbed (Cases 9 to 12, Table 1). At the time of this writing (January, 1958) there have been no new cases for six months.

The Portsmouth Experience

In October, 1957, two cultures of the spinal fluid of infants were recived simultaneously by CDC from Portsmouth, Va. The unclassified Gram-negative bacillus was isolated in each case. Subsequently, checking the records revealed that another culture of the same organism had been submitted for identification in April, 1957. This combination of events was related to the state and local health officers in Virginia, who invited one of us (J. A. B.) to investigate the situation.

A review of the records of two hospitals in Portsmouth brought to light seven cases of fatal meningitis among newborn babies, five of whom were premature. These nurseries each average about 70 premature infants per year. The first four cases, from October, 1956, to April, 1957, were confined to one hospital, while the latter three, from

TABLE 2.—*Portsmouth, Va., Cases of Meningitis Associated with an Unclassified Gram-Negative Bacillus*

Case	Weight, Gm.	Birth Date	Day of Onset After Birth	Day of Death After Onset	Bacteriology *	Cerebrospinal Fluid	Remarks
13	1,616	10/22/56	6	40	CSF, Gram-neg. rod	WBC, 1,008	No autopsy
14	3,062	11/19/56	9	41	CSF, Gram-neg. rod	WBC, 9,028; protein, 460 mg. %	Autopsy, internal hodrocephalus, purulent meningitis
15	2,665	1/18/57	6	10	CSF, Gram-neg. rod	WBC, 13,590; protein, 315 mg. %	Autopsy, purulent meningitis
16	2,495	4/5/57	7	5	CSF, Gram-neg. rod †	WBC, 6,624	Autopsy, purulent meningitis
17	1,985	7/17/57	6	8	CSF, Gram-neg. rod	WBC, 1,683; sugar, 35 mg. %; protein, 126 mg. %	No autopsy
18	1,191	9/23/57	9	17	CSF, Gram-neg. rod †	WBC, 538	No autopsy
19	2,098	10/8/57	5	4	CSF, Gram-neg. rod †	Clotted, purulent	No autopsy

* Negative and positive blood and cerebrospinal fluid cultures are listed.
† Culture identified by the Diagnostic Bacteriology Unit, CDC, as the unclassified organism.

July, 1957, to October, 1957, occurred in the nursery of the second hospital. From the spinal fluid of each of the seven infants an unidentified Gram-negative bacillus had been recovered. Three of these isolations were those studied by CDC and found to be the unclassified organism under question. Cases are presented in Table 2.

Other Isolations

Since 1949 ten cultures of the unclassified organism have been submitted for identification to the Diagnostic Bacteriology Unit, CDC, from states other than Virginia and South Carolina. Only limited clinical information is available on most of the cases from whom cultures were taken, four of which were from Florida, two each from Massachusetts and North Carolina, one from Georgia, and one from Pennsylvania. In eight instances the source of the organism was cerebrospinal fluid. Other isolations were from blood and throat. The ages of the patients are known in six of the cases: five were infants, and one was a 54-year-old man (throat culture).

Clinical and Epidemiological Background

By referring to the cases listed in Tables 1 and 2, one can see that all were newborn babies and that 17 of the 19 were premature. Fifteen died; one recovered without sequallae, and hydrocephalus developed in three of the fatal cases as well as in three survivors. One infant recovered without sequellae. The interval between birth and onset of symptoms is difficult to determine, but by defining onset as first convulsion, cyanotic episode, or sudden deterioration of course some general pattern is suggested. Onsets occurred from the 2d to the 17th day of life, with 16 of the 19 grouped between the 5th and 9th days.

The clinical picture was fairly classic for bacterial meningitis in this age group. A few infants died quickly of sepsis. Only those who survived the acute phase developed true meningial signs.

Since the 19 cases were studied by almost as many physicians, specific clinical details may not be strictly comparable. Table 3 lists the important signs in order of reported frequency. Failure to feed and cyanotic episodes were most prominent. Bulging fontanels, convulsions, and irritability formed a second group. Vomiting and diarrhea were rarely encountered. Actual stiffness of the neck, back, or extremities was present in only four cases. All the infants were maintained in incubators, and so

TABLE 3.—*Clinical Signs in Meningitis Cases in Greenville and Portsmouth*

	Cases, No.
Failure to feed	14
Cyanotic episode	13
Bulging fontanel	10
Convulsion	9
Irritability	8
Failure to gain	7
Jaundice	5
Stiffness in neck, back, limbs	4
Lethargy	3
Vomiting	3
Bleeding tendency	2
Diarrhea	1
Hepatosplenomegaly	0
Rash	0

temperature did not directly reflect the condition of the patient.

The hemogram was not particularly revealing. Studies of the cerebrospinal fluid invariably revealed purulence, and, when these studies were performed, showed elevated protein and depressed sugar. Differential cell counts were not routinely available (Tables 1 and 2).

Certain potential contributory factors, such as race, sex, and weight at birth, were investigated and were found not to differ between the cases with meningitis and the nursery populations in question. Respiratory distress at birth did not occur in all cases. Antibiotics were not routinely used prophylactically, nor was maternal infection or prolonged or difficult labor a uniform experience.

In Greenville on several occasions limited bacteriological surveys of fomites, contacts, and infants were undertaken to explore the source and spread of infection. In a period following the discovery of two cases (July 24 to 29, 1957, and Aug. 12) cultures were taken from personnel in the delivery room and nursery for premature infants and from fomites and other possible infective sources, with no isolation of the unclassified organism. During this period, however, examination of the well babies in the nursery, between 14 and 16 in number, revealed positive throat cultures on five occasions from 4 infants. These infants have remained well.

A more prolonged survey was carried out from Sept. 12 to Oct. 1, 1957, almost three months after the last case of meningitis had been isolated. Studies were conducted on premature and full-term babies, on all personnel, and on the vaginal flora of pregnant women and mothers. On no occasion was the organism encountered.

Bacteriology

A complete description of the bacteriology will be published separately.[5] Briefly, the organism is a long pleomorphic Gram-negative nonmotile bacillus. Colonies when viewed through a hand lens are translucent, smooth, and glistening, while under stereoscopic microscopy they appear translucent with opaque streaks, giving a mottled appearance. The organism is not fastidious and will ferment certain carbohydrates, but only after one week in nutrient broth base. The bacillus is oxidase-positive and a weak indole producer (only when 2% tryptone broth is used and the extraction is made with xylene after 48 hours and overlaid with Ehrlich's reagent). On triple sugar iron slant the medium turns alkaline, and while no H_2S is produced in the stab it may be demonstrated by suspending a lead acetate paper over the slant. The bacillus is generally resistant to antimicrobial agents. When tested by the disc method, with use of maximum concentrations, the organism showed some sensitivity to erythromycin and carbomycin. Biochemical and growth properties are summarized in Table 4.

TABLE 4.—*Properties and Reactions of the Unclassified Bacterium*

Fermentation (nutrient broth):		
Glucose + 1 - 2 wk.	MacConkey-pos.,	Morph., long Filamentous rod
Maltose + 1 - 2 wk.	delayed at 1° isolation	
Xylose neg. at 3 wk.	S. S., neg.	Isolation, Gram-neg
Manitol + 1 - 3 wk.	Urea, neg.	Spores, neg.
Lactose + 1 - 3 wk.	Nitrate, neg.	O_2 requirement, facultative
Sucrose neg. at 3 wk.	Indole, pos.	Temp., 25 to 37 C
	H_2S, pos.	Pigment, neg.*
No fermentation ever before 7 days	MR/VP, neg.	Oxidase, pos.
	Gelatin, pos.	Hemolysis, neg.
	Litmus milk, peptonized	Motility, neg.
		Catalase, pos.

* Yellow strains have been encountered which are closely related to this organism. Sources of this pigmented bacillus reveal its ecology to differ markedly from the bacterium under discussion.

Since the organism is one that is not known to clinicians and bacteriologists, it has been on occasion called Hemophilus influenzae, non-pigment-producing Pseudomonas aeruginosa, Alcaligenes faecalis, or of the tribe Mimeae. Its lack of fastidious growth requirements separates it from Hemophilus influenzae. Since it never occurs as a coccus, it can be excluded from the Mimeae. Fermentation of carbohydrates after one week rules out the Alcaligenes group. A positive indole reaction, failure to produce ammonia, and nonmotility distinguish it from Pseudomonas aeruginosa. With this combination of characteristics, attempts to classify the organism according

to one of the groupings in "Bergey's Manual of Determinative Bacteriology" [6] have thus far been unsuccessful.

Comment

The occurrence of bacterial meningitis in comparatively small nurseries involving 17 premature infants and 2 full-term babies over a period of one year is at variance with previous medical experience. Kagan et al.,[1] reviewing 7129 births in 20 years at the Sarah Morris Premature Center in Chicago, reported only 12 cases of meningitis. Combined figures from the Children's Hospital of Michigan (1949-1954) and Hospital for Sick Children, Toronto (1949-1955), reported by Watson,[2] revealed a total of 45 cases of meningitis occurring before the age of one month, of which only 13 were in premature infants. In two-thirds of the cases in these series organisms belonging to the coliform group were the causative agents. While Gram-negative bacilli were isolated on 17 occasions from the 12 cases in Greenville and the 7 in Portsmouth, none belonged to the coliform group. The organisms recovered from seven of the infants studied by the Diagnostic Bacteriology Unit, CDC, were found to be identical in appearance and biochemical reactions. This bacterium has been encountered in cultures submitted from five other states since 1949, but as yet it has not been satisfactorily placed in any of Bergey's classifications.

It may be hazardous to presume that the 7 cases from which the unclassified Gram-negative bacillus was recovered were related to the 12 in which the exact bacteriology has not been elucidated. The fact, however, that all cases occurred over a comparatively short period of time, in the same nurseries, and with similar symptomology supports this assumption. Further, in 10 of the 12 instances an unidentified Gram-negative bacillus was isolated from cerebrospinal fluid or blood.

Little is known of the ecology of the disease. As yet, limited attempts to isolate the organism from the environment or from human contacts have been unsuccessful. Since the cases have all been confined to nurseries, to this extent the disease resembles a hospital infection. During a period immediately following the occurrence of cases, the bacterium was recovered from the throats of well babies. In a meningitis-free interval the organism seemed to have disappeared from the hospital milieu. While it is tempting to relate these outbreaks to similar experiences described in the literature concerning hospital epidemics of Staphylococcus and Escherichia coli, it is difficult to ascribe a definite pattern from these preliminary data.

Summary

Two outbreaks of meningitis caused by an unclassified Gram-negative bacillus affecting primarily premature infants in hospital nurseries are presented. Other isolations of the organism and its bacteriology are described. Clinical and epidemiological data are discussed.

The following persons aided in this study: G. E. McDaniel, M.D., State Epidemiologist, South Carolina State Board of Health; Mason Romaine, M.D., State Epidemiologist, Virginia State Department of Health; Samuel A. Graham, M.D., Director of Public Health, Portsmouth, Va.; Mr. Robert E. Toomey, Director, Greenville General Hospital, Greenville, S. C.; the medical staff and bacteriologists at the Greenville General Hospital, the Portsmouth General Hospital, and Maryview Hospital, and Bruce Dull, M.D., and Jennie Rakich, R.N., of the Epidemiology Branch.

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Long-Term Study of One Hundred Five Patients with Cystic Fibrosis

Studies Made Over a Five- to Fourteen-Year Period

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The survival beyond childhood of patients with cystic fibrosis is being noted with increasing frequency. This is explained by improved diagnostic methods, with the early recognition of mild cases, and by the application of effective therapeutic measures. The largest number of survivors beyond the age of 10 included in one report is in that of McIntosh.[1] However, there have been no reports dealing with the results of long-term care provided to a large group of patients with cystic fibrosis. It is obvious that the end-results of such a study would reflect diagnostic acumen, for the earlier the case is recognized and the milder the disease the better should be the end-result. It is for this reason that we have introduced a system of clinical evaluation which can be used as a measuring device to compare one patient with the next. It is well, also, to point out some of the reasons why we believe that some cases of this disease are not diagnosed in early life: (1) the belief that this is a rare disease which usually terminates with a fatal outcome in infancy or early childhood, (2) the relatively recent recognition of this disease as a specific entity and unfamiliarity with the wide range of its clinical manifestations, (3) the difficulty in the past of establishing a diagnosis on sound laboratory evidence, and (4) the failure to appreciate the varying degrees of severity with different degrees of involvement of the most commonly affected organs.

The purpose of this study is to present our experience with patients observed and treated over a long period of time.*

The 105 patients have been observed for a minimal period of five years from the time of diagnosis. We included all patients seen by us during a 17-month period beginning Jan. 1, 1956, who fulfilled our only requirement for inclusion in this study, namely, a five-year minimal period of observation. A few patients were not included because we lacked recent detailed observations of our own. One patient in this group is now 25 years of age. We have excluded from consideration a large number of patients over 5 years of age (approximately 200) because their condition had been diagnosed within the past five years. Our oldest patient in this group is 33 years of age and the father of three children. Another patient is Case 11 of McIntosh's report; she is now 16 3/12 years of age; her condition was diagnosed at 6 weeks of age and is considered a mild case. Nor have we included patients followed for more than five years who died prior to Jan. 1, 1956.

Approximately 50% of the patients in this study were hospitalized at the time of the initial diagnosis. This included the 10 patients with meconium ileus who were admitted in the first few days of life. The diagnosis of cystic fibrosis was made in 11 patients prior to referral to us, and in the others the diagnosis was established at their first visit or shortly thereafter. Duodenal intubation was performed in all patients, and the fluid was examined for viscosity, trypsin, and pH in all cases, in the majority of cases for amylase, and lipase, and in a small number for chymotrypsin. In all questionable cases, especially those that were

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* A number of physicians assisted us in the care of these patients, especially Drs. Pincus Catzel, Richard R. Dooley, Ann Evans, Fred Guilmette, Sami Kassim, Paul Patterson, Marie Stoppelman, and Charles Weill.

classified as having partial pancreatic insufficiency, repeat intubations were performed a number of times. The initial duodenal fluid sample showed complete absence of enzymes in 84 patients, whereas in 21 patients partial pancreatic insufficiency or normal enzyme activity was noted. In five of these latter patients progression to complete loss of pancreatic enzyme activity was subsequently noted. Beginning in July, 1954, the sweat test was performed, as devised by Shwachman, Dooley, and Higgins.[8] A plastic bag was employed, and the sweat collection was made from the patient's back onto a weighed 3 in. square gauze pad. This test was performed in 65 patients and showed the characteristic elevations of sodium and chloride concentration. Patients seen after August, 1956, were tested by the finger imprint method for chloride,[8] and the test was strongly positive in each of 93 patients tested. As a rule the patients were seen at regular two- to three-month intervals, or more frequently if necessary, and were encouraged to consult with us on the telephone. A few patients were seen at longer intervals because they lived at a great distance. At each visit a medical history and physical examination was done. Appropriate laboratory examinations and therapeutic suggestions were made. Roentgenograms of the chest were taken at approximately yearly intervals or more frequently if indicated.

Treatment

The general principles of therapy were more or less uniform, with emphasis on individualization. Since antibiotic agents proved effective therapeutically, a brief statement as to their use will be given. Prior to September, 1948, sulfonamides, penicillin, and streptomycin were the only agents available. Penicillin and streptomycin were used primarily during acute exacerbations of pulmonary infections and were given intramuscularily or by aerosol. In a number of instances the sulfonamide drugs were given "prophylactically" over prolonged periods. The beneficial effect of chlortetracycline (Aureomycin) was noted in September, 1948, and it has proved to be one of the most effective antibiotic agents in the treatment of cystic fibrosis.[4]† Oxytetracycline (Terramycin) was introduced early in 1950 and has been equally effective.[5] In many patients tetracycline hydrochloride appears to be less effective than chlortetracycline and oxytetracycline and has been used in milder cases or under special circumstances. Chloramphenicol and erythromycin have been used liberally during the past three years, and novobiocin, only sparingly during the past year. Neomycin administration by aerosol has been employed almost as frequently as penicillin and streptomycin aerosols during the last two years.

Apart from the advent of new antibiotics (since the introduction of chlortetracycline in 1948) the treatment plan has improved further with the addition of nebulization and wetting agents. We shall not present a detailed account of therapy, much of which has been presented elsewhere.[2] In general, we aim to educate the parents,[6] provide constant medical supervision, and employ broad-spectrum antibiotics in prophylactic dosage when there is minimal pulmonary involvement or in therapeutic dosage when the pulmonary infection is well established. Eighty-seven of the one hundred five patients were given antibiotics daily, whereas fourteen patients were given antibiotics intermittently. We have defined intermittent therapy as consisting of less than 8 months of therapy during a 12-month period. Four patients were given antibiotics only when having symptoms of respiratory infection, which was rather infrequent. One antibiotic was used in 80 patients, and combinations of two or more antibiotics, in 20 patients. Chlortetracycline was the most frequently used single antibiotic; the dosage varied from 10 to 25 mg. per kilogram per day. It was also given for the longest period of time, i. e., more than eight years in 10 patients. Oxytetracycline was used singly in 9 patients and in 12 patients was alternated with chlortetracycline in the same dosage schedule. The combination of erythromycin and chloramphenicol was given to 16 patients, to 4 of them for more than three years and to 9 patients for more than two years. More recently we have used aerosol

† Dr. Stanton Hardy, of the Lederle Laboratories Division, American Cyanamid Company, provided a supply of chlortetracycline.

solutions containing, in addition to the antibiotics, propylene glycol, glycerin, and detergents (Triton A-20) for short-term inhalation therapy, with apparently satisfactory results. At present we have no accurate method of assessing the effectiveness of these combined forms of inhalation therapy. In a small number of patients we have used continuous nebulization by placing the child in a tent with constant nebulization throughout the night.[7] These measures have been introduced too recently to influence the results reported. Other therapeutic measures included the use of iodides, bronchodilators, postural drainage, and exercises to improve ventilatory capacity.

The treatment aimed at improving nutrition consisted of a liberal diet in which a relatively high protein intake was emphasized, and an effort was made to reduce the total fat intake. In practically all patients with pancreatic insufficiency substitution therapy with pancreatin (Viokase) was given with each meal. Water-miscible multivitamin preparations were given in twice the usual dosage. Vitamin B complex was used liberally.

Clinical Evaluation

In an effort to determine the severity of the disease and the effect of therapy in any one patient, and in order to compare one patient with the next, a system of clinical evaluation was devised. The final evaluation was derived from an appraisal of each of the four following categories: (1) general activity, (2) physical findings, (3) nutritional status, and (4) findings on chest roentgenograms. Each item was given equal weight, namely, 25 points. A total of 100 points represents a perfect score. The grading was done independently by us. In the beginning there were a number of discrepancies, but these seemed to decrease as our experience increased. The variation was not greater than seven points in any one patient. A detailed account of the items considered in our scoring system is given in Table 1. The status of the patient is considered excellent when the score is over 85, good when the score is between 71 and 85, mild when between 56 and 70, moderate between 41 and 55, and severe when 40 or below. The scoring was made without con-

TABLE 1.—*System of Clinical Evaluation of the Patients with Cystic Fibrosis*

Grading	Points	General Activity	Physical Examination	Nutrition	X-Ray Findings
Excellent (86–100)	25	Full normal activity; plays ball, goes to school regularly, etc.	Normal; no cough; pulse and respirations normal; clear lungs; good posture	Maintains weight and height at above 25th percentile; well-formed stools, almost normal; good muscle mass and tone	Clear lung fields
Good (71–85)	20	Lacks endurance and tires at end of day; good school attendance	Resting pulse and respirations normal; rare coughing or clearing of throat; no clubbing; clear lungs; minimal emphysema	Weight and height at approximately 15th to 20th percentile; stools slightly abnormal; fair muscle tone and mass	Minimal accentuation of bronchovascular markings; early emphysema
Mild (56–70)	15	May rest voluntarily during the day; tires easily after exertion; fair school attendance	Occasional cough, perhaps in morning upon rising; respirations slightly elevated; mild emphysema; coarse breath sounds; rarely localized rales; early clubbing	Weight and height above 3d percentile; stools usually abnormal, large, and poorly formed; very little, if any, abdominal distention; poor muscle tone with reduced muscle mass	Mild emphysema with patchy atelectasis; increased bronchovascular markings
Moderate (41–55)	10	Home teacher; dyspneic after short walk; rests a great deal	Frequent cough, usually productive; chest retraction; moderate emphysema; may have chest deformity; rales usually present; clubbing 2 to 3+	Weight and height below 3d percentile; poorly formed, bulky, fatty, offensive stools; flabby muscles and reduced mass; abdominal distention mild to moderate	Moderate emphysema; widespread areas of atelectasis with superimposed areas of infection; minimal bronchial ectasia
Severe (40 or below)	5	Orthopneic, confined to bed or chair	Severe coughing spells; tachypnea with tachycardia and extensive pulmonary changes; may show signs of right-sided cardiac failure; clubbing 3 to 4+	Malnutrition marked; large protuberant abdomen; rectal prolapse, large, foul, frequent, fatty movements	Extensive changes with pulmonary obstructive phenomena and infection lobar atelectasis and bronchiectasis

sideration of the therapeutic regimen in use at the time. This, in effect, means that the initial scores were determined prior to therapy and the recent ones after years of therapy, and in most cases during therapy.

The information needed to obtain the evaluation must be critically appraised. This is particularly true when one is dealing with the general activity of the patient. On the whole, the less we rely on subjective evidence the more reliable is our evaluation. The scoring has also been of considerable prognostic assistance, as will be pointed out.

Presentation of Material

The 105 patients were followed from 5 to 14 years from the time the diagnosis of cystic fibrosis was established (Table 2).

TABLE 2.—*Duration of Follow-Up of 105 Patients with Cystic Fibrosis*

Follow-Up Period, Yr.	Boys	Girls	Total No. of Patients	Died *	
				M	F
5	10	8	18	2	1
6	12	9	21		1
7	11	13	24		2
8	10	5	15		2
9	4	4	8		
10	7	2	9		
11	2	1	3	1	
12	2	2	4		
13	0	0	0		
14	1	2	3	1	
Total	80	46	105	4	6

* This refers to the period Jan. 1, 1956, to June 1, 1957.

Ninety-five of these patients are still living, and ten have died. Three patients died during the 5th year of follow-up; one, in the 6th; two, in the 7th; two, in the 8th; one, in the 11th, and one, in the 14th. These 10 deaths occurred during the 17th-month period of Jan. 1, 1956, to June 1, 1957. The longest period of observation extends 14 years for three patients.

We shall present the patients in seven groups, divided arbitrarily according to the age at which the diagnosis was made. Table 3 lists the number of patients in each of these groups. All patients in Group I had meconium ileus and were relieved of their obstruction surgically, with one exception (Patient 10). Note from Table 3 that 41 patients were diagnosed as having cystic fibrosis after their second birthday, and nine patients were diagnosed after the age of 8 years. The ages of the patients as of June 1, 1957, are also listed in Table 3. Thirty-one patients are between the ages of 5 and 8 years; twenty-eight, between 8 and 10 years; thirty-six, between 10 and 15 years, and ten, over 15 years.

We should like to comment briefly on each of these seven groups. The first group comprises those patients with meconium ileus. A detailed report on the outcome of patients with meconium ileus was recently made.[8] The survival in any one patient following surgical correction of the obstruction depends on the severity and the progression of the pulmonary involvement. In the nine survivors over the age of 5 the pulmonary status was considered good during the first month of life. The one patient with moderate pulmonary involvement in early infancy died at the age of $8\frac{8}{12}$ years as a result of extensive bronchiectasis. The initial

TABLE 3.—*Long-Term Follow-Up of 105 Patients with Cystic Fibrosis Arranged in Seven Groups According to Age at Diagnosis*

Serial No. of Patients	Age at Diagnosis	Group	Patients, No.	Died	Present Age of Patients (June 1, 1945), Yr.			
					5 to 8	8 to 10	10 to 15	Over 15
1-10	Birth (M. I.)*	I	10	1	6	2 (1)	1	1
11-31	1 wk. to 6 mo.	II	21	3	13 (2)†	6	2 (1)	0
32-46	6 mo. to 1 yr.	III	15	0	5	5	5	0
47-64	1 to 2 yr.	IV	18	3	5 (1)	8 (1)	4 (1)	1
65-85	2 to 4 yr.	V	21	0	2	7	12	0
86-96	4 to 8 yr.	VI	11	1	0	0	10 (1)	1
97-105	8 to 16 yr.	VII	9	2	0	0	2 (1)	7 (1)
Total			105	10	31 (3)	28 (2)	36 (4)	10 (1)

* Meconium ileus.
† Number of patients who died is given in parentheses.

scoring of these cases of meconium ileus was not attempted. However, the present scores of the nine living patients are as follows: excellent in one patient, good in three patients, mild in three patients, and moderate in two patients.

In the 21 patients listed in Group II the diagnosis was made during the first six months of life. The oldest patient is $12\frac{1}{12}$ years and the youngest is $5\frac{8}{12}$ years of age. Three patients died, all as a result of advanced pulmonary changes. The scores of the remaining 18 patients are as follows: good in eight, mild in seven, and moderate in three. We attempted a comparison of the present conditions of the patients with their conditions at the time of diagnosis. We found that the conditions of the three patients who died at ages 14, $7\frac{4}{12}$, and $5\frac{3}{12}$ was originally considered moderate in two cases and mild in the other case. Nine patients have improved. Six patients are in the same category, which indicates that they have not shown significant progression of their disease under therapy, whereas three patients are worse in spite of our best efforts. Of considerable interest is the observation that two patients now show normal chest roentgenograms, in spite of initial chest involvement in one patient. All patients in this group have been receiving constant antibiotic therapy. Of the 18 living patients, 9 have not required hospitalization during the past five years, 6 were hospitalized once, and 3 were hospitalized twice.

The 15 patients in Group III were diagnosed as having cystic fibrosis between the ages of 6 months and 1 year. The oldest patient is now 13 years of age, and the youngest, $5\frac{1}{2}$ years. Nine patients are now better than when first seen; two show no deterioration of their condition, and four are worse. Eight cases are rated as good; four, as mild; two, as moderate, and one, as severe. When the rating was calculated on the basis of the patients' conditions at the time of diagnosis they were as follows: one excellent, two good, eight mild, and four moderate. During the past five years three patients in this group were hospitalized on one occasion, one with heat prostration and two with bronchopneumonia. One child was hospitalized on two occasions, once for dental extraction and again as a result of a severe reaction to a bee sting.

There are 18 patients in Group IV. The diagnosis in each case was made between 1 and 2 years of age. The oldest patient is $16\frac{4}{12}$ years. Three patients in this group died at ages $12\frac{7}{12}$, $9\frac{1}{2}$, and $7\frac{10}{12}$ years, respectively. Four patients are over 11 years of age; seven are between 8 and 10 years, and four are between 5 and 8 years. At the present time seven patients are better than when their disease was diagnosed, five are about the same, and three are worse. The present ratings of the 15 patients are as follows: one excellent, four good, six mild, and four moderate. During the past five years 4 of the 15 living patients required hospitalization on one occasion, one for abdominal exploration because of a suspicious mass which turned out to be impacted feces, another because of the development of diabetes, one for treatment of dehydration, and the fourth because of extensive pulmonary infection.

Twenty-one patients are placed in Group V, as their conditions were diagnosed between the ages of 2 and 4 years. Twelve patients in this group are over 10 years of age, the oldest being $14\frac{11}{12}$ and the youngest, $7\frac{3}{12}$ years. At present 12 patients are better, 5 are about the same, and 4 are worse in comparison with their condition at the time of diagnosis. Of the present ratings, one is excellent; three are good; seven, mild; nine, moderate, and one, severe. Each of eight patients in this group was hospitalized on one occasion during the past five years. One patient in this group, now $12\frac{1}{2}$ years of age, had a segmental resection of the right lower lobe when $3\frac{3}{12}$ years of age, because of bronchiectasis. In spite of this operation, there was no improvement in his condition until the age of $6\frac{1}{2}$ years, when the diagnosis of cystic fibrosis was confirmed and proper treatment was introduced. At present he is rated as being a mild case and is included in our separate

study dealing with resections of pulmonary lesions in cystic fibrosis.[9]

In the 11 patients in Group VI the diagnosis was made between the ages of 4 and 8 years. One child died at the age of $10\frac{9}{12}$ years with extensive pulmonary changes. The postmortem examination revealed partial pancreatic involvement, a condition recognized in this youngster for approximately five years prior to death. The oldest patient is $15\frac{11}{12}$ years, and the youngest, 10 years of age. The present conditions of the 10 patients are as follows: one excellent, one good, three mild, and five moderate. One patient of this group was hospitalized because of bronchopneumonia, and one patient who died was hospitalized five times during his last two years of life.

Group VII includes nine patients whose conditions were diagnosed between the ages of 8 and 16 years, as listed in Table 4. This table gives the age at the time of diagnosis, the present age, our clinical evaluation at the time of diagnosis, and our present evaluation. The two patients with the lowest scores have died. Three patients are now worse than initially; two are the same, and two, better. The present rating

TABLE 4.—*Initial and Present Clinical Evaluation of the Nine Patients of Group VII Diagnosed Between the Ages of Seven and Sixteen Years*

Patient	Rating and Age, Yr.	Clinical Evaluation				Total Score
		Activity	Physical Examination	Nutrition	Chest Films	
97	Initial (7 10/12)	12	13	11	12	48
	Present (17 11/12)	20	16	14	10	60
98	Initial (9 4/12)	15	12	15	12	54
	Present (15 6/12)	7	10	10	8	35
99	Initial (8 10/12)	15	16	13	11	55
	Present (14 10/12)	15	13	11	9	48
100	Initial (9 0/12)	20	17	13	11	61
	Present (16 8/12)*	6	10	8	8	32
101	Initial (8 4/12)	16	14	12	9	52
	Present (13 8/12)*	8	8	7	7	30
102	Initial (10 2/12)	20	17	16	14	67
	Present (16 6/12)	15	11	14	10	50
103	Initial (12 2/12)	18	17	16	14	65
	Present (18 4/12)	22	20	23	20	85
104	Initial (12 10/12)	24	21	25	15	85
	Present (19 7/12)	24	22	23	13	82
105	Initial (15 11/12)	24	23	25	9	81
	Present (22 11/12)	22	20	22	12	76

* Rating done approximately one to two months prior to death.

TABLE 5.—*Summary of Clinical Status of 105 Patients After Five to Fourteen Years of Treatment, on June 1, 1957*

Group	Age Range at Diagnosis	Patients in Group, No.	Progress			
			Better	Stationary	Worse	Dead
I	M. I.*	10	7	0	2	1
II	0 to 6 mo.	21	9	6	3	3
III	6 to 12 mo.	15	9	2	4	0
IV	1 to 2 yr.	18	7	5	3	3
V	2 to 4 yr.	21	12	5	4	0
VI	4 to 8 yr.	11	1	7	2	1
VII	Over 8 yr.	9	2	2	3	2
	Total	105	47	27	21	10

* Meconium ileus.

TABLE 6.—*Comparison of Initial and Present Ratings*

	Cases, No.	Excellent	Good	Mild	Moderate	Severe	Died
Initial rating	95 *	4	10	44	33	4	..
Present rating	105	6	28	29	30	2	10

* Ten patients with meconium ileus are not included in the initial rating.

TABLE 7.—*Yearly Rating (Last Five Years) in Three Patients Who Died*

Patient	Age at Death, Yr.	Age at Diagnosis	Period & Age of Rating	Rating				
				Activity	Physical Examination	Nutrition	Chest X-Rays	Total Score
29	14	10 wk.	Initial 3/12	12	13	12	14	51
			1952 10 8/12	20	20	12	15	67
			1953 11 8/12	16	17	11	14	58
			1954 12 8/12	16	16	12	12	56
			1955 13 9/12	13	12	12	10	47
			1956 14	13	8	8	7	35
30	7 4/12	8 wk.	Initial 3/12	11	10	10	13	44
			1952 3	15	11	12	11	49
			1953 4	11	10	11	12	44
			1954 5	14	13	12	10	49
			1955 6	10	9	8	8	35
			1956 7 3/12	6	6	4	5	21
63	9 1/12	1 6/12 yr.	Initial 1 6/12	17	15	20	13	65
			1952 5	22	19	22	17	80
			1953 6	22	18	19	14	73
			1954 7	20	16	17	11	64
			1955 8	15	14	16	9	54
			1956 9	8	10	12	7	37

of the seven patients is as follows: three are good, one is mild, two are moderate, and one is severe. Six patients were hospitalized during the past five years, and three have not been hospitalized since the establishment of the diagnosis.

Table 5 summarizes the clinical status of the 105 patients. It can be seen that 47 patients are better, 27 are the same, 21 are worse, and 10 have died. The age of the patient at the time of diagnosis, as indicated in the various groups, does not appear to reflect any special trend insofar as the outcome is concerned. In each age group we find essentially similar responses, some patients showing improvement, some being the same, and others being worse. In the group of 47 patients who are now better, 3 are in excellent condition; the condition of 20 is good; of 22, mild, and of 2, moderate. Of the group of 27 patients who are the same, the present condition is excellent in two, good in nine, mild in nine, and moderate in seven patients.

A comparison of the present clinical status of the 95 living patients with that at the time of diagnosis is summarized in Table 6. Four patients were in excellent condition at the time of the diagnosis, and six are now in excellent condition. At the time of the diagnosis 10 patients were in the "good" category, and at present 28 patients are in this category. There are fewer cases in the mild and moderate categories. During the last five-year period of observation no patient from the excellent and good groups ended up in the severe category. On the other hand, three patients initially noted as having severe disease are now in the mild group. Nine patients went from the moderate to the severe group, and the conditions of three went from mild to severe. Of the 10 patients who died, none were originally in the excellent or good group. Four were originally in the mild category; three, in the moderate group, and three, in the severe group.

In order to appraise the course of the disease in those patients who died, a yearly rating was calculated for three patients during their last five years of life, as shown in Table 7. In these patients, as was noted in all patients in this group, initial improvement followed institution of therapy. The duration of the improved state lasted nearly twelve years in Patient 29, four years in Patient 30, and six years in Patient 63. The rating shows a uniform decline in all categories as the disease progresses in severity.

Comment

The widely held belief that cystic fibrosis of the pancreas is inevitably a fatal disease in infancy or early childhood is not substantiated by our experience. As in many newly described disease entities the patients who are first described as presenting the so-called classical features are the most ad-

vanced cases and may represent a segment of the total disease picture when viewed retrospectively. This is the case with cystic fibrosis. We no longer can justifiably say that "this patient looks too well to have cystic fibrosis," a statement so often made and often proved wrong. In addition, we now recognize patients as having this disease who were formerly excluded on the basis of having normal or partial pancreatic function.

The recognition of this disease as a separate entity resulted from the investigations of pathologists, notably Farber, Wolbach, and Andersen. Inasmuch as their material consisted primarily of infants who died, we can readily understand the conclusions reached from this experience. Andersen's report in 1938 [10] included 20 cases from the pathologic files of the Babies Hospital. Sixteen patients died before 6 months of age; one, between 6 months and 1 year; two, between 1 and 1½ years, and one, at 3 years 1 month. The age at death of the oldest patient she found in the literature was 14½ years, a patient reported by Parmelee in 1935.[11] It must be remembered that few living patients with this disease had been recognized at the time of her report. In Farber's experience at the Boston Children's Hospital the average age at death of a large number of patients with cystic fibrosis prior to 1948 was 12 months. The infants who died in the neonatal period with meconium ileus were excluded. Bodian [12] more recently pointed out that 53 of 68 fatal cases in his series of 116 were under 2 years of age and 15 were 2 to 13 years of age.

These figures must be contrasted with those given in this report as well as in the reports of McIntosh,[1] di Sant'Agnese,[13] Royce,[14] and others, where the age of diagnosis of previously untreated patients is beyond infancy. Indeed, the impression may be gained that if a child with this disease survives infancy his case is mild. This, however, is not always true, as can be seen from an appraisal of the patients in this report. Our ability to recognize mild forms of this disease stems from increased clinical awareness and improved diagnostic laboratory methods. In the series of patients included in this report, approximately 20 would have been excluded by others as questionable cases because our criteria at the time of diagnosis did not meet the rigid concept calling for complete pancreatic insufficiency. Although these patients were diagnosed and treated prior to the development of the most useful diagnostic test, the sweat test, we took into account an array of evidence, namely, the positive family histories, quantitative assay of a multitude of pancreatic enzymes found in the duodenal fluid, the physical properties of the duodenal fluid, and, in many instances, the degree of response of the pancreas to a functional stimulation, in addition to the entire clinical picture, which included an appraisal of the type of pulmonary leson. This aspect of cystic fibrosis has been presented by us elsewhere [15] and by Gibbs [16] and di Sant'Agnese.[17]

In view of the varying degrees of severity of this disease, statements concerning the effectiveness of any form of therapy must be made with caution and with the above facts in mind. It is for this reason that we have attempted to assess the severity of illness by using easily available clinical and laboratory yardsticks. It is clear that the effect of pulmonary involvement reflects the severity of the disease, inasmuch as the cause of death is eventually pulmonary insufficiency from a combination of diffuse obstructive phenomena and infection. We therefore feel that the major criteria employed in the evaluation of severity should be based on assessment of pulmonary function or its derangement. As mentioned above, the duration of life prior to diagnosis is no measure of severity of the disease, although it is obvious that the patients with severer cases would have died in infancy. The report of our patients who have survived the five-year period of follow-up does not automatically exclude all the severe cases. Many of our cases were diagnosed in infancy and were considered severe at the time. The inclusion of nine

patients with meconium ileus requiring surgery indicates that we have included the worst prognostic group of former years.

The effectiveness of therapy in a large group of patients with cystic fibrosis may be indicated by the extension of life achieved. In the postmortem data of Farber and Craig,[18] the age of death of our fatal cases has been extended from an average of 12 months prior to 1948 to 59 months for the period 1951 through 1956. There were 40 postmortem examinations during this six-year period, and in each case the diagnosis was made clinically and confirmed by the pathologist. The number of patients who died at less than one year of age is 11. Fourteen patients died between the ages of 1 to 5 years, and sixteen patients died after their fifth birthdays.

Royce,[14] in his attempt to rate patients on a clinical basis, gave equal weight to the following: exercise tolerance, cough, breathing, clubbing of the digits, and chest auscultation. Although we include these features in our Table, the emphasis is not on individual symptoms but rather on a more-inclusive appraisal of the patient's condition. For example, we do not feel that clubbing per se accurately reflects the extent of the pulmonary lesion. As can be seen from our classification, coughing, breathing, clubbing, and chest auscultation would come under one heading, namely, the physical examination. The physical examination receives equal weight with our interpretation of the chest x-ray, the general activity of the patient, and the nutritional status of the patient. At present, we find our system useful and realize that more accurate method of assessment may become available, particularly if we include objective rather than subjective evidence. Inasmuch as pulmonary-function studies cannot be explored to the same extent in infants and small children, we may be able to apply such measurements as residual volume, total lung capacity, maximum breathing capacity, and lung resistance and compliance, to our patients over 5 years of age and use these measurements as a more accurate yardstick than our clinical impressions. Studies along this line are being pursued by our colleagues Cook et al.[19] One reason for seeking a reliable yardstick is to determine and appraise therapeutic measures. We believe that the results presented indicate the effectiveness of the medical regimen employed. Considerable improvement is needed not only in our therapeutic measures but also in calling attention to the need for recognizing mild or early cases and pursuing a planned program of therapy. As further investigations yield information concerning the mechanism and the chemical characteristics of the abnormal secretions, it may be possible to improve upon our present therapy. We feel that our policy of energetic therapy has improved the patient's clinical condition. At the same time it results in an economic advantage, since repeated, prolonged, and expensive hospitalizations have been avoided. The effectiveness of any long range therapeutic program depends so much on the cooperation of parents as well as on their financial, intellectual, and emotional make-up.

Summary

A series of 105 patients with cystic fibrosis of the pancrease studied over a 5- to 14-year period is presented. The diagnostic criteria and the therapy employed are briefly outlined. The patients are divided into seven groups according to the age at time of diagnosis. Ten patients had meconium ileus, and their cases were accordingly diagnosed within the first few days of life. In 21 patients diagnosis was made at less than 6 months of age. In 15 patients diagnosis was made between 6 months and 1 year; in 18, between 1 and 2 years; in 32, between 2 and 8 years, and in 9, between 8 and 16 years. At the present time 41 patients are over 10 years of age. Ten of the one hundred five patients died during the period January, 1956, to June 1, 1957, when this study was terminated.

A system of clinical evaluation for the patients affected with cystic fibrosis is presented and is based on the following criteria:

the general activity of the patient, the findings on physical examination, the nutritional status, and the findings on the roentgenogram of the chest. Each of these four items is given equal weight in a scoring system in which 100 represents a perfect score. It was felt that a scoring system to establish the degree of severity of cystic fibrosis was needed in view of the marked variation in the clinical manifestations of the disease.

The results of a carefully supervised therapeutic program are presented in table form. The present conditions of the ninety-five patients in comparison with their original status is as follows: Forty-seven patients are now better, twenty-seven are about the same, and twenty-one are worse. We should like to emphasize the value of pursuing a vigorous therapeutic program in a disease which is still so little understood. As a better understanding is achieved, more effective therapeutic methods may become available. In our series of 105 patients the diagnosis was made after the age of 3 years in 28%. It is hoped that the improved diagnostic tests now available will result in early diagnosis and prompt institution of effective therapeutic measures.

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The Effect of Graded Doses of Vitamin D on the Serum Calcium and Phosphorus Levels

The Influences of Varying Doses of Vitamin D on the Incidence of Hypocalcemia During the First Week of Life

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It has been established by several investigators that infants fed cow's milk formulae during the first week of life tend to develop lower serum calcium and higher phosphorus levels than infants fed breast milk.[1-4] Vitamin D administered in physiologic doses, i. e., 600 U. S. P. units per day during the first week of life, aggravates this tendency.[5] Hypocalcemia has also been observed on the first day of life before any feedings have been given.[6-10]

Since hypocalcemia of varying etiology has been successfully treated with large doses of vitamin D,[11-17] we studied the effect of graded doses of vitamin D on the serum calcium and phosphorus levels and the incidence of hypocalcemia occurring during the first week of life.

Patient Material and Methods

All infants studied were normal newborn infants who received a processed milk formula of isocaloric nature, containing 77 mg. of calcium and 51 mg. of phosphorus per 100 cc. of formula.

The infants were divided into six groups. Ninety-three infants in Group I (control group) received no vitamin D. Fifty-two infants in Group II received a milk formula which resulted in a total dosage for the five-day study period of 400 U. S. P. units. The infants of Groups III to VI received an additional single oral dose on Day 1 of the study period, as follows:

Group III, 30 infants, 3000 U. S. P. units
Group IV, 19 infants, 13,000 U. S. P. units
Group V, 51 infants, 45,000 U. S. P. units
Group VI, 115 infants, 200,000 U. S. P. units

Serum calcium and phosphorus were determined on the first day of life before any feedings were given and on the day of discharge. The period of observation in all groups was between five and six days. In some infants of Group VI the period of observation extended to 21 to 42 days. Calcium and inorganic phosphorus determinations were made on sera obtained by venipuncture and were performed by the ultramicrochemical methods described by Sobel.[18,19]

Results

Tables 1 and 2 show the effect of graded doses of vitamin D on the mean serum calcium and phosphorus concentrations, respectively. There is a statistically significant fall of the mean serum calcium from Day 1 to Day 5 in all groups of infants with the exception of Group V, which received 45,000 U. S. P. units of vitamin D. There is a statistically significant rise of the mean serum phosphorus from Day 1 to Day 5 in all groups.

Tables 3 and 4 present a statistical analysis of the serum calcium and phosphorus changes from Day 1 to Day 5 in Groups I, II, III, IV, V, and VI by setting up six contingency tables comparing Groups I and II, I and III, II and III, I and IV, I and V, and I and VI. There is a statistically significant change of calcium in each pair compared. However, the changes in Groups II, III, and IV are in the direction of fall and those in Groups V and VI are in the direction of rise (Table 5). There is no

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TABLE 1.—*A Comparison of the Mean Concentration of Serum Calcium on the First Day with That of the Day of Discharge in Newborn Infants Fed Graded Amounts of Vitamin D*

Vitamin D, U. S. P. Units	Infants, No.	Age, Days	Ca, Mg./100 Ml. Range	Mean	S. D.	χ^2	*P* Value
0	93	1	8.2-11.0	9.3	0.56	23.4	<0.01
		5	6.1-10.6	8.8	0.87		
400	52	1	8.0-11.4	9.1	0.84	3.1	<0.09
		5	4.8-10.7	8.6	0.99		
3,000	30	1	8.2-10.0	9.1	0.46	12.3	<0.01
		5	5.2- 9.8	8.2	1.06		
13,000	19	1	8.3-10.2	9.0	0.48	6.9	<0.01
		5	6.7-10.7	8.5	0.99		
45,000	51	1	8.0-10.9	9.4	0.61	2.28	<0.95>0.9
		5	7.4-10.4	9.4	0.53		
200,000	115	1	8.0-11.0	9.3	0.72	8.5	<0.01
		5	7.0-10.5	9.0	0.72		

TABLE 2.—*A Comparison of the Mean Concentration of Serum Phosphorus on the First Day with That of the Day of Discharge in Newborn Infants Fed Graded Amounts of Vitamin D*

Vitamin D, U. S. P. Units	Infants, No.	Age, Days	P, Mg./100 Ml. Range	Mean	S. D.	χ^2	*P* Value
0	93	1	4.1- 7.9	5.8	0.74	11.5	<0.01
		5	5.7-10.1	7.8	0.87		
400	52	1	2.7- 7.0	5.1	0.92	22.4	<0.01
		5	4.2- 9.6	7.5	1.04		
3,000	30	1	4.7- 8.5	6.1	0.86	3.8	<0.05
		5	5.8-10.3	7.9	0.92		
13,000	19	1	4.8- 7.2	5.9	0.75	16.4	<0.01
		5	6.5- 9.6	7.9	0.80		
45,000	51	1	3.4- 7.2	5.6	0.91	40.5	<0.01
		5	5.3-11.0	7.5	1.12		
200,000	115	1	3.2-10.1	6.8	1.53	12.0	<0.01
		5	4.9-10.8	7.9	1.04		

significant change in the prosphorus when the groups are compared.

Table 6 shows the incidence of hypocalcemia * in all groups receiving varying amounts of vitamin D. The percentages of infants developing hypocalcemia when no vitamin D was given and when 400 U. S. P. units of vitamin D were administered are approximately the same, i. e., 16.1% and 17.3%, respectively. The percentage is higher in the infants of Group III, receiving 3000 U. S. P. units of vitamin D during their stay at the hospital (30%). It falls to 16% when 13,000 U. S. P. units are administered. It is lowest in the groups of infants receiving 45,000 and 200,000 U. S. P. units of vitamin D, 2% and 5.2%, respectively.

Tables 7 and 8 show the effect of regimens with and without vitamin D supplement on the mean serum calcium and phosphorus concentration on the fifth day in two groups of infants who had hypocalcemia on the first day of life. There is

* Hypocalcemia is defined as a level of 7.9 mg. per 100 ml. or lower.

TABLE 3.—*Statistical Analysis of Changes in Serum Calcium During First Five Days of Life on Regimens of Powdered Milk With and Without Vitamin D Supplement*

Group *	$Ca_5-Ca_1>0.1$ †	$Ca_5-Ca_1<0.1$ †	Total
I	62	31	93
II	15	37	52
Total	77	68	145
$\chi^2=7.2$		P ‡<0.01	
Group	$Ca_5-Ca_1>-0.15$	$Ca_5-Ca_1<-0.15$	Total
I	71	22	93
III	9	21	30
Total	80	43	123
$\chi^2=21.2$		P<0.01	
Group	$Ca_5-Ca_1>-0.45$	$Ca_5-Ca_1<-0.45$	Total
II	32	20	52
III	10	20	30
Total	42	40	82
$\chi^2=6.1$		P<0.02>0.01	
Group	$Ca_5-Ca_1>0.05$	$Ca_5-Ca_1<0.05$	Total
I	62	31	93
IV	5	14	19
Total	67	45	112
$\chi^2=10.8$		P<0.01	
Group	$Ca_5-Ca_1>0.2$	$Ca_5-Ca_1<0.2$	Total
I	61	32	93
V	18	33	51
Total	79	65	144
$\chi^2=12.2$		P<0.01	
Group	$Ca_5-Ca_1>0$	$Ca_5-Ca_1<0$	Total
I	67	26	93
VI	38	77	115
Total	105	103	208
$\chi^2=33.6$		P<0.01	

TABLE 4.—*Statistical Analysis of Changes in Serum Phosphorus During First Five Days of Life on Regimen of Powdered Milk With and Without Vitamin D Supplement* *

Group	$P_5-P_1>2.25$	$P_5-P_1<2.25$	Total
I	40	53	92
II	31	21	52
Total	71	73	144
$\chi^2=3.56$		P<0.1>0.05	
Group	$P_5-P_1>1.7$	$P_5-P_1<1.7$	Total
I	57	35	92
III	14	16	30
Total	71	51	122
$\chi^2=2.52$		P<0.9>0.1	
Group	$P_5-P_1>1.95$	$P_5-P_1<1.95$	Total
II	31	21	52
III	14	16	30
Total	45	37	82
$\chi^2=1.35$		P<0.9>0.1	
Group	$P_5-P_1>2.1$	$P_5-P_1<2.1$	Total
I	44	48	92
IV	10	9	19
Total	54	57	111
$\chi^2=0.14$		P<0.7	
Group	$P_5-P_1>2.4$	$P_5-P_1<2.4$	Total
I	35	57	92
V	20	31	51
Total	55	88	143
$\chi^2=0$		P=0.99	
Group	$P_5-P_1>1.8$	$P_5-P_1<1.8$	Total
I	55	37	92
VI	76	41	117
Total	131	78	209
$\chi^2=0.58$		P<0.4>0.3	

* Group I received no vitamin D; Group II, 400 U. S. P. units of vitamin D; Group III, 3000 U. S. P. units of vitamin D; Group IV, 13,000 U. S. P. units of vitamin D; Group V, 45,000 U. S. P. units of vitamin D; Group VI, 200,000 U. S. P. units of vitamin D.

† Ca_5, serum calcium levels on the fifth day of life; Ca_1, serum calcium levels on the first day of life; P_5, serum phosphorus levels on the fifth day of life; P_1, serum phosphorus levels on the first day of life. Differences in calcium and phosphorus levels are expressed in milligrams per 100 ml.

‡ P is for one degree of freedom. The distribution of serum calcium and phosphorus changes from Day 1 to Day 5 in Groups I, II, III, IV, V, and VI was examined by setting up six contingency tables, [20] comparing Groups I and II, Groups I and III, Groups II and III, Groups I and IV, Groups I and V, and Groups I and VI. The critical values of serum calcium and serum phosphorus were selected by determining the median change in serum calcium and serum phosphorus in each pair of groups.

* See footnote to Table 3.

TABLE 5.—*The Direction of Change in the Mean Serum Calcium on the Fifth Day of Life in Groups Receiving Graded Doses of Vitamin D as Compared with the Group Receiving no Vitamin D Supplement*

Group *	Mean Ca, 5th Day, Mg./100 Ml.	Mean Difference, Mg./100 Ml.	% Difference
I	8.8		
II	8.6		
III	8.2		
IV	8.5		
V	9.4		
VI	9.0		
I vs. II		−0.2	−3
I vs. III		−0.6	−7
I vs. IV		−0.3	−3
I vs. V		+0.6	+7
I vs. VI		+0.2	+3

* See footnote to Table 3.

a statistically significant rise of the mean serum calcium and phosphorus concentrations in both groups.

Table 9 presents a statistical analysis of serum calcium and prosphorus changes from Day 1 to Day 5 in two groups of infants who had hypocalcemia on the first day by setting up two contingency tables and comparing the vitamin D-treated group with the untreated group. The differences in serum calcium changes are statistically significant, while the difference in serum phosphorus changes is not statistically significant.

Table 10 shows that the incidence of hypocalcemia on the fifth day of life in a group of infants who were hypocalcemic on

the first day and who received no vitamin D during their stay was 43%, while in a similar group of hypocalcemic infants receiving 200,000 units of vitamin D the incidence was 12.1%.

Table 11 presents serial determinations of both calcium and phosphorus at weekly intervals in 18 infants who received 200,000 U. S. P. units of vitamin D on the first day of life. The period of observation varied from 21 to 42 days. No instance of hypercalcemia was observed during their stay at the hospital.

The serum urea levels were normal, and no instance of vomiting or constipation was observed in this group.

TABLE 6.—*Incidence of Hypocalcemia Occurring During the First Week of Life in Infants Fed Graded Amounts of Vitamin D*

Vitamin D, U. S. P. Units	Infants, No.	No. Who Developed Hypocalcemia	Per Cent
0	93	15	16.1
400	52	9	17.3
3,000	30	9	30
13,000	19	3	16
45,000	51	1	2
200,000	115	6	5.2

TABLE 7.—*A Comparison of the Mean Serum Calcium Concentrations on the Fifth Day of Life in Two Groups of Infants Who Had Hypocalcemia on the First Day of Life on Regimens With and Without Vitamin D Supplement*

Vitamin D, U. S. P. Units	Infants, No.	Age, Days	Ca, Mg./100 Ml. Range	Mean	S. D.	χ^2	*P* Value
0	42	1	6.0- 7.9	7.4	0.47	13.8	<0.01
		5	5.9-10.0	7.9	0.99		
200,000	33	1	6.0- 7.9	7.3	0.47	45.7	<0.01
		5	6.1-11.2	8.7	1.08		

TABLE 8.—*A Comparison of the Mean Serum Phosphorus Concentrations on the Fifth Day of Life in Two Groups of Infants Who Had Hypocalcemia on the First Day of Life on Regimens With and Without Vitamin D Supplement*

Vitamin D, U. S. P. Units	Infants, No.	Age, Days	P, Mg./100 Ml. Range	Mean	S. D.	χ^2	*P* Value
0	42	1	3.5-10.5	6.5	1.34	27.4	<0.01
		5	2.5-13.0	8.0	1.40		
200,000	33	1	2.1- 9.7	5.9	1.51	17.6	<0.01
		5	4.8- 9.8	7.7	1.22		

TABLE 9.—*Statistical Analysis of Changes in Serum Calcium and Phosphorus During First Five Days of Life in Two Groups of Infants Who Had Hypocalcemia on the First Day of Life on Regimens With and Without Vitamin D Supplement* *

Group	$Ca_5-Ca_1>0.9$	$Ca_5-Ca_1<0.9$	Total
No vitamin D	25	8	33
200,000 U. S. P. Units	13	29	42
Total	38	37	75
$\chi^2=14.9$	$P<0.01$		
Group	$P_5-P_1>1.9$	$P_5-P_1<1.9$	**Total**
No vitamin D	18	14	32
200,000 U. S. P. units	17	22	39
Total	35	36	71
$\chi^2=1.2$	$P<0.9>0.1$		

* See footnote to Table 3.

TABLE 10.—*A Comparison of the Incidence of Hypocalcemia at the End of the First Week in Infants Who Had Hypocalcemia on the First Day of Life and Received 200,000 U. S. P. Units of Vitamin D and Those Who Received No Vitamin D.*

Infants, No.	Vitamin D, U. S. P. Units	Hypocalcemia on Day 5 or 6	%
42	0	18	43
33	200,000	4	12.1

TABLE 11.—*Serial Values of Serum Ca and P in Infants Who Received 200,000 U. S. P. Units of Vitamin D*

	Calcium and Phosphorus, Mg./100 Ml.						
	Initial	6 Days	13 Days	21 Days	28 Days	35 Days	42 Days
Ca	7.7	9.0	9.2	9.0			
P	6.4	5.1	7.3	7.4			
Ca	10.0	9.4	10.2	9.6			
P	....	....	8.5	8.1			
Ca	8.8	8.4	8.8	8.6			
P	5.9	9.5	7.1	6.7			
Ca	7.6	9.0	8.4	8.8	9.2	10.2	
P	6.5	7.4	6.4	7.6	6.6	6.0	
Ca	7.0	9.6	10.2	9.6	9.4		
P	5.1	6.4	8.0	7.1	7.5		
Ca	7.4	7.0	8.4				
P	6.8	8.5	7.7				
Ca	6.0	8.0	8.4	9.0	8.8	8.7	
P	4.0	6.4	7.0	6.5	7.3	6.3	
Ca	6.0	7.0	7.8				
P	5.8	8.2	10.1				
Ca	10.2	7.6	8.8				
P	6.0	8.0	7.6				
Ca	8.2	9.0	9.6	8.8			
P	5.1	6.6	7.9	7.4			
Ca	9.6	9.8	9.9	8.8			
P	4.7	8.4	8.0	8.0			
Ca	7.0	8.2	8.5	9.0	8.8	8.9	8.5
P	7.2	8.3	7.4	8.4	6.7	7.6	6.8
Ca	7.6	8.6	9.6				
P	7.9	7.4	7.9				
Ca	7.0	11.2	8.9	8.5	8.4		
P	7.9	4.8	7.4	6.7	6.6		
Ca	8.0	8.8	8.2				
P	5.7	7.1	9.6				
Ca	9.0	8.6	8.6				
P	5.3	6.9	6.5				
Ca	8.8	9.2	9.0				
P	....	7.1	7.0				
Ca	7.6	7.0	7.8	8.0	9.6	9.3	9.5
P	2.1	9.6	6.8	6.9	6.6	7.0	7.0

Comment

The data obtained in this study would tend to substantiate the view that the action of vitamin D on the serum calcium varies with the dosage.[14,20-23] During the first week of life small amounts of vitamin D tend to aggravate the fall of the serum calcium levels.[6] The administration of increasing doses of vitamin D negates this effect. The incidence of hypocalcemia rises from 16.1% when no vitamin D is given to an incidence of 30% when 3000 U. S. P. units are administered and then falls to 2% when 45,000 units are given.

Since it is generally accepted that vitamin D increases the absorption of calcium from the intestinal tract and thus tends to raise the serum calcium levels when a hypocalcemic state exists, the effect of vitamin D in physiologic doses during the neonatal period is paradoxical.

Klein and Gow believe that vitamin D inhibits the secretion of parathyroid hormone but that it does not block its actions on the renal tubules once it is secreted.[23] This view offers a possible explanation for the paradoxical effect of small doses of vitamin D in the early neonatal period if it is assumed that a hypoparathyroid state of varying degree exists during this period. The action of vitamin D would be to diminish the secretion of an already poorly functioning parathyroid gland and thus tend to decrease the calcium level.

Massive doses of vitamin D tend to increase the absorption of calcium and perhaps of phosphorus from the gastrointestinal tract and also are said to act directly on bone, liberating lime salts into the circulation.[20,21] This effect may account for the rise of the serum calcium levels when the dose of vitamin D was raised to 45,000 U. S. P. units.

The mean phosphorus levels rose significantly in all groups of infants at the end of the first week of observation. In 8 of 16 cases studied serially the phosphorus level (Table 11) fell during the second week, and in some, during the third and fourth weeks. An explanation for the failure to

observe a consistent fall in the serum phosphorus level in the infants receiving large amounts of vitamin D may be found in observations made by several investigators [24-26] that in instances of hypoparathyroidism the serum phosphorus levels may be normal or slightly elevated at first while the serum calcium drops at once. Also, in instances of hypoparathyroidism treated with massive doses of vitamin D both the serum calcium and phosphorus rise at first, and it is only after a varying period of treatment that the serum phosphorus tends to fall.[12,27,28] This effect of large amounts of vitamin D on phosphorus homeostasis has been attributed to the possible increased absorption of phosphorus from the intestinal tract and also to the liberation of phosphate from bone into the circulation.[21] The gradual fall in serum phosphorus is effected through the rather slow action of vitamin D on the glomerular filtration of phosphorus.[20,29] A time factor is of importance before this effect on the phosphorus level is discernible. Since the periods of observations have been relatively short—in most instances two weeks—the effect on phosphorus homeostasis cannot be accurately assessed.

Summary

Graded doses of vitamin D were given during the first week of life to infants on a processed milk formula. Serum calcium and phosphorus were determined on the day of birth and on the day of discharge. Three thousand U. S. P. units of vitamin D aggravated the tendency toward the development of hypocalcemia and significantly lowered the mean calcium serum levels. Forty-five thousand and two hundred thousand U. S. P. units negated this tendency.

Two hundred thousand U. S. P. units of vitamin D raised the mean serum calcium levels and markedly diminished the incidence of hypocalcemia on the day of discharge in infants who were hypocalcemic on the day of birth.

No incidence of hypercalcemia was observed in 18 of the infants who received a single dose of 200,000 units of vitamin D during the first day of life. Urea levels remained normal, and no gastrointestinal upsets were noted in those infants.

The pediatric house officers and the nursing staff of the Newborn Nurseries of the Jewish Hospital of Brooklyn aided in this study. Endo Products, Inc. Richmond Hill, N. Y. supplied the water-miscible vitamin D product, containing 100,000 U. S. P. units per cubic centimeter.

Jewish Hospital of Brooklyn, 555 Prospect Place.

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Abnormal Amino Acid Metabolism in a Case Suggesting Autism

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Examination of urine samples from patients exhibiting various incompletely described diseases recently revealed an abnormality in amino acid excretion in a child affected by a severe mental condition suggesting autism. This abnormality in amino acid excretion was also detected in the younger sibling of the patient, although the sibling has not displayed any abnormal mental effects to the present time. Further investigations of the patient demonstrated a deviation in the decarboxylation pathways of tryptophan metabolism, probably secondary to some other metabolic alteration.

A number of studies in recent years have clearly demonstrated the relationship between body chemistry and mental function. In the case of phenylketonuria there is no longer any doubt that specific inherited alterations in the metabolism of phenylalanine are responsible for the oligophrenia found in affected persons, as demonstrated by regression or prevention of the mental abnormalities when susceptible persons are placed on a phenylalanine-free diet.[1-3] There is also an increasing body of evidence for biochemical abnormalities in certain psychoses, although here a clear demonstration of cause and effect has yet to be achieved. For example, certain types of mental disease have been shown to be associated with high blood ceruloplasmin and low ascorbic acid.[4] The striking mental effects produced by lysergic acid diethylamide and by reserpine, and the demonstration that the action of reserpine is through 5-hydroxytryptamine (serotonin), a normal brain metabolite,[5] have given rise to suggestions that schizophrenia may result from an alteration in the metabolic pathway tryptophan → 5-hydroxytryptophan → 5-hydroxytryptamine → 5-hydroxyindole-3-acetic acid.[6]

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Report of a Case

The patient was first seen at the University Hospital on Oct. 1, 1956, at the age of 18 months. An accompanying letter and hospital summary indicated that she had received a fairly extensive investigation when 15 months of age, at Children's Hospital of San Francisco. The attending physician's impression was "possible convulsive seizures of undetermined origin." It was felt that the child's behavior was "very much that of a psychotic; it is not quite autism but certainly borders on it." * The attendants were unable to obtain a 24-hour urine specimen during her short stay in the hospital and therefore could not perform the total amino acid nitrogen determination.[6a]

The patient was the second of three girls in a pediatrician's family, the other two children appearing normal in all respects. Pregnancy and neonatal history were normal, and she progressed satisfactorily during infancy. She rolled over at 3 months, sat unsupported at 6 months, crawled at 9 months, walked at 13 months, and was saying "Mama" and "Dada" at 13 months and also "patty-caking." Her parents felt that in general her physical and mental development was advanced in comparison with the oldest girl.

At 9 months of age spasmodic twisting movements of the eyes and face were first noted. Occasionally she would throw her head back. These "seizures" lasted only a few seconds, with no loss of consciousness and no after-effect. She seemed perfectly normal between attacks. The frequency of these seizures increased from 1 per week to approximately 40 to 50 per day at 14 to 15 months of age. An EEG at this time did not "show an abnormal amount of frequency of slow activity. However, the slow cycles at times occur in se-

* Thelander, H. C.: Personal communication to the authors.

quences and are of fairly high voltage, suggesting paroxysmal abnormal electrical activity, diffusely in the cortex." The seizures then gradually diminished till, when the patient was seen here at 18 months, they were four to five per day and consisted of a simple twitching of the eyelids and holding the hands before the eyes. When the patient was 13 months of age the parents began noting a gradual change in her personality with an associated mental regression over the next four to five months. This mental regression reached the point where even her parents went unrecognized.

When she was examined by us at the age of 18 months, there were no specific physical abnormalities. She was a well-developed blonde girl who weighed 28 lb. and was 33 in. tall. She was a most self-centered child, with a seeming unawareness and certainly disinterest in her environment. Her waking hours were spent in bed rocking, staring into space, and playing with her hands, the last usually associated with a constant gibberish but with no meaningful words and no attempt to communicate. She was irritable when disturbed, but in general there was a lack of affect, brief emotional outbursts being related mainly to hunger and withdrawal of food once offered. A vague smile could occasionally be elicited.

Family history revealed that one cousin had "cerebral palsy resulting from a birth injury." There was no indication of any disease similar to that of the patient for at least two generations.

Our initial impression was that the patient's abnormality was convulsive disorder with subsequent mental retardation.

Ferric chloride test for phenylpyruvic acid was negative. Hemoglobin was 12.8 gm.; RBC, 3,900,000; WBC, 7600, with a normal differential count. Skull x-rays were normal. Psychometrics confirmed our impression that the patient was functioning at a retarded level, approximately 4 to 6 months. The examiner felt that the pattern obtained was similar to that produced by the "nonstimulated child." On psychiatric evaluation the patient was considered an autistic child, and here, too, the question of lack of stimulation was raised. The EEG at this time was interpreted as being normal.

The patient was observed over a period of seven months. This included three hospital admissions for specific investigation plus numerous clinic visits. We did not feel that there was any change in her personality or mental status.

Experimental Methods

Examination of the urine for amino acids was by means of two-dimensional paper chromatography, with use of phenol and lutidine as the solvent pair.[7] The amino acids were made visible by dipping the chromatogram into 0.2% 1,2,3-triketohydrindene (ninhydrin) in 95% ethanol, followed by heating at 95 C for seven minutes. Quantitative estimates were made by comparing the reflectance of the urine spots with those obtained from standards run under similar conditions. Indole derivatives were studied on two-dimensional chromatograms by the procedure of Dalgliesh,[8] with use of ultraviolet light (3660 A.) and Ehrlich's reagent as the means of detection. Quantitative estimates of kynurenine, indoleacetic acid, and indolelactic acid were obtained from a series of one-dimensional chromatograms on which aliquots of urine were compared to known quantities of the appropriate standard compound. The solvents used were butanol-ethanol-1 N HCl (4:1:1) for kynurenine and indoleacetic acid and isopropanol-NH_4OH-H_2O (8:1:1) for indolelactic acid. Ehrlich's reagent was used to reveal the spots. Indoleacetic acid was used as the standard for indolelactic acid. Although this chromatographic method involves considerable error, it was deemed adequate to demonstrate that successful loading with tryptophan had occurred. The quantitative colorimetric test of Udenfriend, Titus, and Weissbach[9] was used to measure 5-hydroxyindoleacetic acid. Phenolic compounds were studied by the method of Armstrong, Shaw, and Wall.[10]

Results

As part of the initial screening for abnormal levels of metabolites, five urine samples from the patient, six from her sibling, and one from each of the parents were examined for amino acids and for phenolic compounds. In samples from the two children, but not in those from the parents, a striking departure from normal was observed on the amino acid chromatograms. This consisted in very low levels of glutamine (undetectable in several samples) and consistent excretion of a triketohydrindene-positive substance indistinguishable chromatographically from γ-aminobutyric acid. In addition, there was a moderate increase in glutamic acid, although levels did not exceed the range occasionally observed in essentially normal samples. No abnormalities were noted on the chromatograms of phenolic acids.

Since the metabolism of γ-aminobutyric acid, glutamic acid, and glutamine—all important constituents of brain tissue—is

dependent on pyridoxine (vitamin B_6)-catalyzed reactions to a large extent, an attempt was made to assess the vitamin B_6 status of the patient to eliminate a possibly undetected vitamin B_6 deficiency. Accordingly, the patient was hospitalized and after three days on a constant diet was given 3.25 gm. of L-tryptophan orally (0.25 gm. per kilogram of body weight). A 20-month-old boy (Subject 1) receiving physical therapy following recovery from poliomyelitis served as a control, consuming the same diet and receiving 3.50 gm. of L-tryptophan as a test load. The total volume of urine excreted was collected, in the case of the female patient, by catheterization. Following the tryptophan load the control patient was discharged from the hospital, but the affected patient remained on the constant diet, receiving a supplement of 2 gm. of L-glutamine per day for three days, followed by a day with no supplement, then a supplement of 25 mg. of pyridoxine per day for three days. Following the pyridoxine supplement, an attempt was made to load the patient again with tryptophan, but this time without success because of the unpleasant taste of so large a quantity.

Examination of the urine samples collected throughout the experimental period revealed that, on the hospital diet, the amino acid pattern returned more nearly to normal, there still remaining an increase in the γ-aminobutyric acid and a slight deficiency of glutamine. On addition of glutamine to the diet, the glutamine excretion became entirely normal and remained so throughout the period of observation. The glutamine and pyridoxine supplements had no other detectable effects.

Analysis of the urine formed during the tryptophan load revealed several striking differences between the affected patient and the control. Although most of the tryptophan metabolites occurred in the two samples in comparable quantities, the patient failed to excrete detectable amounts of indoleacetic acid, idolelactic acid, and unchanged tryptophan. The excretion of metabolites characteristic of the kynurenine pathway, including xanthurenic and kynurenic acids, was very similar in the two subjects.

The interpretation of these differences with respect to the clinical status of the patient required the testing of additional subjects. Accordingly, three more children were given 0.25 gm. of L-tryptophan per kilogram, one of whom (Subject 2) was a 46-month-old girl hospitalized for esophageal reconstruction and the other two of whom (Subjects 3 and 4) were healthy children, 36 and 44 months old, respectively. The patient was also retested four months after the initial test period. These test periods consisted of collection of timed urine samples one to two days prior to the administration of the tryptophan and collection of at least one sample on the day following the tryptophan. The tryptophan was administered with breakfast and soon after voiding. The first five-hour sample after the tryptophan load was lost for Subject 4, and the quantities of tryptophan metabolites reported for her consequently represent minimum values.

A very large number of tryptophan metabolites were excreted after ingestion of the test load. Examination of chromatograms suggested no differences between the patient and the controls for most of these substances; hence they will not be discussed in detail. Among the substances detected, in addition to indoleacetic acid, indolelactic acid, and kynurenine, were xanthurenic acid, kynurenic acid, acetylkynurenine, 3-hydroxykynurenine, acetyl-3-hydroxykynurenine, and anthranilic acid, as well as a number of substances whose identity was not established. These identifications were based primarily on the chromatographic "maps" of Dalgliesh [8] and on parallel runs with those known substances which are available. Tryptophan was detectable in most samples, but the amount varied widely among the five subjects, suggesting possible differences in renal threshold for this substance. The excretion of tryptophan was not

TABLE 1.—*Urinary Excretion of Tryptophan Metabolites Following a Test Load of* L-*Tryptophan* *

Subject	L-Tryptophan Ingested, Millimoles	Urinary Excretion, Millimoles			
		Kynurenine	Indoleacetic Acid	Indolelactic Acid	5-Hydroxy-indoleacetic Acid
Patient					
Test I	17.2	5.3	0.00	0.0	0.003
Test II	17.2	0.8	0.05	0.4	0.003
1	18.5	4.4	0.15	1.7	0.021
2	16.0	0.5	0.13	0.6	0.012
3	14.8	0.4	0.14	0.4	0.010
4	19.7	0.8 †	0.16 †	1.0 †	0.007

* Test load, 0.25 gm. L-tryptophan per kilogram of body weight.
† The first five-hour sample following ingestion of tryptophan was lost for this subject; hence, these represent minimum values.

associated with the disease status of the patient.

The results for some of the substances are presented in Table 1. It will be noted that the kynurenine excretion varies approximately tenfold. That this is not due to differences in the amount of tryptophan actually entering the body is indicated by the lack of correlation between kynurenine and other metabolites. In particular, of the two tests on the patient the one which gave the lower yield of kynurenine was the one showing the higher yield of indolelactic and indoleacetic acids. It is of interest to note also that the patient gave the lowest yields of indolelactic acid, indoleacetic acid, and 5-hydroxyindoleacetic acid (5HIAA).

Another indication of the difference in indole metabolism between the patient and the control subjects is given in Table 2. It can be seen here that the excretion rates of 5HIAA are normal for the patient in the absence of a tryptophan load but are not increased very much on the addition of tryptophan. The collection periods shown in Table 2 are the single period for each subject during which he showed his highest excretion rate following the tryptophan load. In the case of the second test of the patient the period shown is the only one in which there was a detectable increase. All the control subjects, however, showed increases of a much longer duration than the four hours of the second test of the patient.

The second tryptophan load of the patient was followed on the third day by a phenylalanine tolerance test (0.1 gm. of L-phenylalanine per kilogram of body weight) according to the test for persons heterozygous for phenylketonuria.[11] The blood and urine levels of phenylalanine and tyrosine following the test load, as studied by paper chromatrography, indicated no impairment of ability to metabolize phenylalanine.

Comment

The limited testing performed on the patient makes any interpretation of the results very tentative. It seems likely, however, that this patient is abnormal in her metabolism of indole compounds. While the test situation is unrealistic physiologically, biochemical stresses of this type have proved useful in detecting partial metabolic blocks in carriers of phenylketonuria, where the limited ability to oxidize phenylalanine becomes apparent only in the presence of an artificially raised phenylalanine level.[11] Thus, even though the patient shows normal levels of indole metabolites in her usual environment, she apparently is limited in her ability to convert large quantities of tryptophan to indolelactic acid, indoleacetic acid, and 5HIAA.

TABLE 2.—*Maximum Rate of Urinary Excretion of 5-Hydroxyindoleacetic Acid Following Ingestion of Tryptophan* *

Subject	Urinary Excretion of 5-Hydroxyindoleacetic Acid, μg./Hr.		Duration of Collection Period Showing Maximum Rate, Hr.
	Normal Av. *	Maximum After Load	
Patient			
Test I	53	75	24
Test II	83	224	4
1	96	660	7
2	137	417	8
3	71	325	4.2
4	66	389	2

* The normal average values given are based on samples collected immediately before and after the test period.

Clark, Weissbach, and Udenfriend [12] have shown that 5-hydroxytryptamine arises from tryptophan via 5-hydroxytryptophan and that the decarboxylation is mediated by a highly specific enzyme. If all the 5HIAA produced as a result of tryptophan loading is derived from 5-hydroxytryptamine, then this would require that the two presumably independent pathways, with and without a 5-hydroxyl group, both be blocked. Such a situation is not likely to arise as a result of a primary enzymatic deficiency of a hereditary nature, since no case is known in which two enzymes are under the control of a single genetic locus. There may be points at which these similar structures could be simultaneously influenced, such as in transport across membranes, where the mechanisms are frequently less specific. This would require the block to be subsequent to tryptophan, since the kynurenine pathway is unaffected. An alternate explanation would be the presence of some inhibitor which affects more than one pathway. For example, it was recently reported that 5-hydroxytryptophan decarboxylase from rat kidney is markedly inhibited by cupric ions.[13] It is conceivable that such inhibition might also exist for the tryptophan decarboxylase and that an increase level of copper is responsible for both phenomena. Indeed, alterations in copper might also be invoked to explain the changes in amino acid excretion, since copper is known to be associated with changes in amino acid metabolism [14] in Wilson's disease and metal chelation is believed to be important in amino acid absorption.[15] It is also possible that some 5HIAA arises from tryptophan by a pathway other than the one indicated, although such pathways have not been demonstrated.[16] Dalgliesh and Dutton [17] have shown that the argentaffin cells are the principal site for the conversion of tryptophan to 5-hydroxytryptophan, the product then being absorbed by other tissues for the further conversion to 5-hydroxytryptamine. It has also been shown that administration of 5-hydroxytryptophan can lead to an increase in brain serotonin and 5HIAA.[5] Since serotonin is known to play an important role in normal mental function, it is obvious that any major alteration in the production or destruction of serotonin will be accompanied by changes in mental function. One may thus speculate that the marked autism observed in the patient is related to her decreased ability to metabolize tryptophan via the 5-hydroxyindole pathway.

The younger sibling of the patient, although originally shown to exhibit the same abnormality of amino acid excretion, has continued to develop normally to the present age of 16 months. It has not been possible to test her ability to metabolize tryptophan. The existence of the amino acid abnormality in two members of a sibship, even though the trait is shown to be variable, raises the question of possible genetic factors involved in the etiology of this disease. It is certainly impossible to draw conclusions on the basis of the present data as to the effects of heredity. Since we do not seem to be dealing with a primary metabolic block, however, it is entirely possible that both children have some inherited enzyme deficiency which, in the patient, is associated with an internal environment such that effects on other metabolic pathways occur. These modifying factors could be either genetic or environmental.

The failure of administered tryptophan to lead to an increase in 5HIAA excretion has led Udenfriend, Titus, Weissbach, and Peterson [16] to conclude that the tryptophan hydroxylating system is operating maximally. This is shown not be the case with our control subjects, who responded with several-fold increases in 5HIAA production. The identity of the product was confirmed by extensive paper chromatographic studies in a variety of solvents using both the nitrosonaphthol reagent of Udenfriend, Titus, and Weissbach [9] and Ehrlich's reagent. Our subjects were very young, however, the oldest being 4 years, and there may be changes with age in the ability to hydroxylate tryptophan. In the two control subjects who were tested in their home environment, alterations in their behavior, in the form of

greater intractability than normal, were remarked on by the parents, who had not been forewarned that the test might have any such effect and who volunteered the information without being asked. While the unscientific nature of this evidence is obvious, it seems probable that the large tryptophan load did induce behavioral changes, possibly by increasing the serotonin levels of the brain.

Summary

Studies with L-tryptophan-loading tests of an 18-month-old girl diagnosed as autistic suggest a decreased ability to metabolize tryptophan via the 5-hydroxyindole pathway to 5-hydroxyindoleacetic acid and also to indolelactic and indoleacetic acids. This is not believed to result from a primary enzymatic block. It is suggested that the mental aberration is a result of an altered ability to maintain normal brain serotonin levels.

Loading normal children with L-tryptophan produced increases in urinary 5-hydroxyindoleacetic acid levels, in contrast to other reports that hydroxylation of tryptophan is maximal with normal levels of tryptophan. These results may be associated with the young age of our subjects.

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Dr. James L. Wilson, of the Department of Pediatrics and Communicable Diseases, referred the patient who was the subject of this study. Todd Schuster, Charles Porter, and Patricia Llewellen gave technical assistance.

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Anal Fissures in Infants and Children

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Pediatric proctologic problems occur with sufficient frequency in medical practice to demand special consideration. Schapiro [1] reported 2700 pediatric proctologic disorders at a general hospital, representing 2.34% of the total pediatric admissions over a 35-year period. Although the literature is replete with material concerning the management of anal fissure, we were prompted to report our series because of the inadequate, though vigorous, therapy that is frequently rendered the pediatric patient. We hope that, by our presenting all facets of the problem, a greater understanding will be achieved and treatment will improve. Five hundred consecutive pediatric proctologic cases were reviewed from our combined practices. A statistical summary of the varied disorders is presented in the Table.

Incidence of Pediatric Proctologic Disorders in 500 Consecutive Patients with Anal Fissures

	Patients, No.
Fissure in ano	206
Adenoma of rectum	56
Constipation without other pathology	49
Ulcerative colitis and proctitis	37
Fecal impaction	25
Prolapse of mucosa	19
Parasites	19
Psychogenic incontinence, no organic disease	18
Internal hemorrhoids	17
Abscess and fistula	14
Foreign bodies	10
Pruritus ani	9
Congenital anomalies	6
Milk allergy	4
Pilonidal cyst	3
Celiac disease	3
Congenital megacolon	3
Presacral teratoma	2

Incidence and Pathogenesis

It can be seen from the table that 206 patients, or 41%, suffered from anal fissure. There were 81 boys and 125 girls. Our figures correspond approximately to those of Mentzer [2] and Murray.[3]

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The patients were placed in three anatomic age categories as described by Schapiro,[1] since it will be shown that the anatomic age of the child has a bearing upon the predisposition to the development of the fissure. The classification is as follows and includes the number of patients with fissure in each group:

	Patients with Fissure, No.
Newborn (Age A):	
birth through 3d month	8
Infant (Age B):	
4th month through 3 years	63
Childhood (Age C):	
3 years through 15 years	135

It can readily be appreciated that fissures were most commonly encountered in the Age C group. In the A and early B groups, the fissures were usually multiple, and in most instances in which single fissures were found they were situated either anteriorly or posteriorly. Only 23 lateral fissures were seen in the entire series, and all of these were in the A and B groups.

It is believed that the primary cause of anal fissure is trauma caused by the passage of hard, bulky stool or by explosive diarrhea. In the age A and B groups the terminal portion of the rectum and the anus form almost a straight line, owing to the poor development of the sacrococcygeal arch. Therefore, trauma is directed to all quadrants of the anus at the same time. This results in multiple fissures, which are more commonly seen in these age groups. In the C group and in adults the sacrococcygeal curve is well developed and the levator ani muscle sling pulls the upper portion of the anal canal forward. The stool is directed primarily in an anteroposterior direction. Because of the decussating fibers

of portions of the external sphincter muscle, a muscular defect in the sphincteric support of the anus is present. These two factors predispose the older group toward anterior or posterior fissures.

Many observers believe that crypt infection plays an important role in the genesis of anal fissure. It is our contention that the fissure occurs initially and that crypt infection may follow.

Clinical Signs and Symptoms

The three most constant symptoms of anal fissue are pain, constipation, and bleeding. In infants and children, the pain arises as the stool is passed and is often accompained by stiffening of the legs, hyperextension of the spine, and crying. The duration of pain after defecation varies considerably. The bleeding may be scanty or profuse. Constipation is one of the commonest associated symptoms in these patients. Of the 206 children, 186 had a history of chronic constipation prior to the development of the fissure. In eliciting a history it would be well to have a clear concept of the true nature of constipation. We believe that constipation is present if the stool is hard, regardless of the frequency of defecation. If the patient has stools at widely separated intervals but the consistency is normal, no constipation exists. It is as illogical that every person should have the same bowel habits as it is that everyone should require the same amount of sleep or food or should wear the same size of clothing. One should not insist that a daily evacuation occur when the patient functions normally with defecation at two- , three- , or four-day intervals. It has been shown repeatedly [4] that no toxic substances are absorbed as a result of retained feces in the unobstructed bowel. It has become an American tradition to defecate regularly, and it is with a great deal of personal pride that adult patients, particularly, extol their own virtue in having a daily scheduled evacuation. Certainly, less emphasis upon frequency and more upon consistency is desirable.

Examination of the patient should be performed in knee-chest, Sims, or prone position under satisfactory illumination. The buttocks are gently separated, and most fissures are readily visible without the necessity of instruments. The acute fissure will have a characteristic elliptical "split lip" appearance. If the fissure has been present for some time, an edematous skin tab, or so-called "sentinel" pile, may be seen distally, and a hypertrophied papilla may be seen proximally, at the crypt level. The latter two findings are caused by an inflammatory reaction. When the fisssure reaches this stage it is called an "anal ulcer." Digital examination may be facilitated by applying a topical anesthetic solution of 10% piperocaine (Metycaine) directly on the fissure so as to minimize the discomfort of the examination. An endoscopic examination should be performed wherever possible, in order to rule out inflammatory intestinal disease. It must be kept in mind that atypical anal ulcers occur in a variety of diseases such as blood dyscrasias, tuberculosis, and skin neoplasms.

Treatment

The management of anal fissures in infants and children is essentially conservative. This is in contrast to the condition in adults, the majority of which cases eventually must undergo surgery.

Of our series of 206 patients, only 5 required surgical intervention because of failure to heal under medical management. One of these occurred in the Age B group, and four, in the Age C group. All of these instances were well-developed anal ulcers with "sentinel" piles and hypertrophied papillae.

Fissures during the first three months of life occasionally may be associated with a congenitally small anus. In such cases gentle dilation of the anus with the finger is efficacious and can ordinarily be accomplished in one or two treatments. This should be performed by the physician and not by the parent. Medical therapy consists of softening the stool, rendering defa-

cation painless, and alleviating fear and apprehension on the part of the child. A variety of stool softeners are available. Any liquid emollient given by mouth will be of benefit. Recently dioctyl sodium sulfosuccinate has been used with success. The application of a topical anesthetic ointment by the mother usually renders defecation painless and therefore relieves some of the apprehension of the child. If a fissure fails to respond within three to four weeks and becomes a chronic anal ulcer, surgery will be necessary.

Although suppositories are the time-honored anorectal panacea, we are strongly opposed to their use. The insertion of a suppository through a spastic, fissured, painful anus increases trauma and engenders fear in the patient. The suppository then melts in the rectal ampulla and works its way upward into the rectosigmoid and sigmoid colon, not downward onto the fissure. It is, therefore, illogical to administer such medication as an analgesic, when it will be in contact with the mucosa above the pectinate line, where no corticospinal sensory nerves are present and where no fissure exists. The stool will be softened by oral medication, and this action of the suppository becomes superfluous.

We do not advise the use of silver nitrate, despite the fact that it is prescribed treatment in most medical and pediatric texts. Silver nitrate is destructive to tissue, causes severe pain, and as a result increases muscle spasm. It is obvious also that its use does not endear the physician to his patient. When the fissure is in the healing phase and defecation is painless, cod liver oil ointment, scarlet red, and a colloidal product prepared by reacting sulfonated *m*-cresol and formaldehyde (Negatan, Lilly) are helpful in promoting healing.

Psychologic Factors

One of the most important factors in the perpetuation of the fissure is the fear that defecation will be painful. It is this fear that causes the child to consciously inhibit defecation, sometimes for several days, despite abdominal cramps and the insistence of well-meaning parents. A hard, dry, bulky stool often results, which prevents healing. When defecation is painless through the use of anesthetic ointment, the frequency of passage increases, fear is eliminated, and the fissure heals.

Constipation, especially between the ages of 2 and 6, is frequently psychogenic.[3] It is during this period that toilet training is initiated. The harmful effects of premature or forceful training cannot be overestimated. The child is undergoing the "anal phase" of sexual development and regards his feces as a proud possession and an integral part of his body. During toilet training, many enthusiastic diaper-weary parents force the child to dispose of his stool as and when the adult wishes. Aggressive hostility is exhibited by constipation. Reinforcement of the problem then occurs when the parent overwhelms the child with suppositories and enemas, increasing the hostile reaction. The final blow to the child is the development of an anal fissue. Therapy will be materially aided if the mother is acquainted with the psychodynamics of constipation and if her own anxiety is relieved.

Summary

A statistical study of 500 consecutive pediatric proctologic patients is reported.

Forty-one per cent, or 206 patients, were seen because of anal fissure.

Pathogenesis is discussed from anatomic, physiologic, and psychogenic points of view.

Conservative management healed fissures in 201 patients. Surgery was necessary in only five patients.

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The Relationship of Little's Disease to Premature Birth

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Introduction

Little's disease is the term applied to morbid states established in infancy or in prenatal time and characterized by varying degrees of bilateral impairment in motility of the extremities and trunk. Babinski signs and enhanced deep tendon reflexes are characters differentiating this disorder from peripheral neuromuscular disorders and from purely dystonic and ataxic conditions. The term is generally used to denote those forms of cerebral palsy variously known as cerebral spastic paralysis, cerebral diplegia, congenital spastic paraplegia, spastic diplegia, and congenital quadriplegic spastic paralysis. There is considerable divergence of opinion in regard to cases which should be included under the heading of Little's disease. Furthermore, a wide variety of disease processes has been considered to be responsible for the disease. Some of these processes are intracranial hemorrhage, anoxia or asphyxia, genetic faults, prenatal degenerative processes, and toxic states.[1-6] Little[7] and many subsequent investigators have been aware of the frequent occurrence of premature birth in groups of patients with Little's disease, but most of these authors (including Little himself) have treated prematurity with no greater emphasis than other abnormal processes of gestation and parturition in the cause of the disease. Several published reports cite prematurity rates at 20% to 40% in series of cases of Little's disease.[8-13] Only Brissaud[14] believed that it was possible to segregate cases of Little's disease into two distinct forms, one of which was caused by prematurity.

Abnormal conditions of pregnancy and labor resulting in high mortality rates have been found to be associated with high rates of morbidity as well.[15] Prematurity certainly is a condition which is associated with high mortality rates.[16] Kohl,[17] in a study of 3538 premature infants, found a mortality of 51.6% in those between 1001 and 1500 gm., 22.2% between 1501 and 2000 gm., and 5.7% between 2001 and 2500 gm.

The present report is based upon an investigation wherein the symptoms and signs of children afflicted with neurologic disorders were correlated with gestational and parturitional factors known to be associated with high rates of infant mortality. The object of the study was to determine whether any one factor was more strongly associated with one type of neurologic disorder than another. This article deals particularly with the relationship of prematurity to different forms of cerebral palsy, mental deficiency, and epilepsy.

Clinical Material and Collection of Data

The presence or absence of neurologic symptoms and signs was recorded in an inclusive manner for all patients with cerebral palsy, epilepsy, and mental deficiency examined by me; a few had other neurologic conditions. There was a total of 562 patients, ranging in age between 2 and 20 years. All but a few came from homes in the region of Detroit and were from families with good standards of nutrition and health. Most of the data regarding physical findings and background history had been tabulated before the relationship of birth weight to any particular set of neurologic signs was suspected. The suspicion of a significant relationship between birth weight and Little's disease emerged from a preliminary inspection of

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From the Division of Neurology, Henry Ford Hospital.

the data; subsequently, therefore, all patients presenting the chief complaint of impaired motor function were examined and assigned to a diagnostic category before history was obtained.

Data regarding the general factors associated with gestation and birth were obtained from the parents or from hospital records. Data regarding birth weight, with which this study is particularly concerned, are believed to be accurate. Granting the presence of inaccuracies, it seems unlikely that these were such as to introduce bias.

Analysis of the Data

The 562 cases were divided into two groups according to the presence or absence of the combination of the following findings in the individuals (Table): (1) bilateral Babinski signs, (2) hyperactive deep tendon reflexes, (3) increased (usually) or decreased muscular tonus, (4) reduced motility of extremities and trunk, and (5) onset of walking later than 14 months of age. The combination of these five manifestations, for the sake of convenience, will be referred to by the code symbol "D" (diplegia). Combinations of manifestations other than the five listed above will be referred to by the code symbol "O" (other). Among the cases assigned to the group with D manifestations were persons with one or more additional symptoms and signs, as follows: (1) convulsive seizures, (2) definite mental deficiency (or I. Q. less than 70), (3) athetotic or ataxic movements, (4) positive tonic neck reaction, (5) definite asymmetry of extremity function, (6) greater impairment of upper than of lower extremity function, and (7) hypotonicity of musculature. These will be refered to by the code symbol "C" (complex). The absence of C manifestations in cases assigned to the D group will be referrred to by the symbol "S" (spastic). Thus, among the group with D manifestations (diplegia) there were cases with D plus C manifestations (D+C, complex diplegia) and cases with D plus S manifestations (D+S, simple spastic diplegia).

Patient Grouping

Group O (454 patients):
All lack bilateral Babinski signs,
but have epilepsy, mental deficiency, hemiplegia, etc.

Group D (76 patients):
All have bilateral Babinski signs,
Little's disease

Subgroup D+C (42 patients), with any of the C symptoms or signs (complex diplegia)	Subgroup D+S (34 patients), with no C symptoms or signs; lower extremities principally involved (simple spastic diplegia)
1. Convulsions 2. Mental deficiency 3. Athetosis or ataxia 4. Tonic neck reaction 5. Asymmetry of extremity function 6. Greater impairment of upper than of lower extremities 7. Hypotonicity	

There were assigned to the O group 483 patients, the birth weight being known in

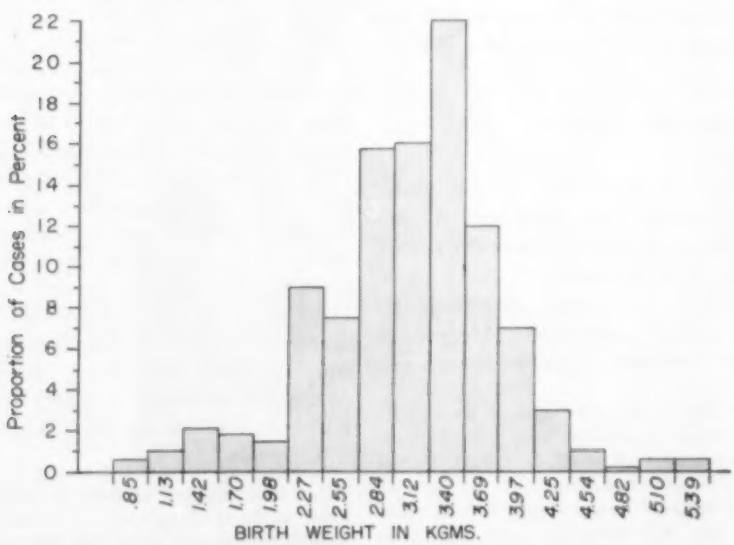

Fig. 1.—Birth weights of 454 Group O cases. These patients had neurologic disorders other than Little's disease and lacked signs conventionally identified with bilateral corticospinal (pyramidal) tract damage. Mean birth weight was 3245 gm. (7 lb. 3 oz.).

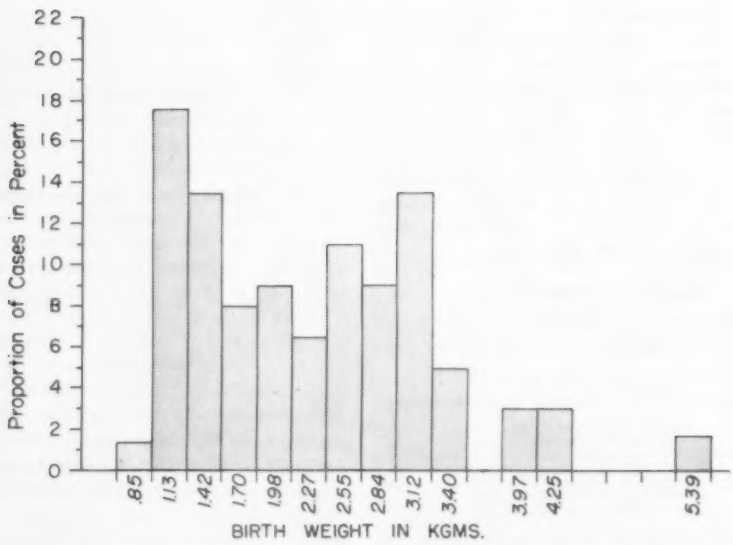

Fig. 2.—Birth weights of 76 Group D cases. These patients had Little's disease and had signs conventionally identified with bilateral involvement of the corticospinal or pyramidal tracts. Mean birth weight was 2392 gm. (5 lb. 4 oz.).

454. There were 79 patients in the D group, the birth weight being known in 76. Patients in whom birth weight was not known were excluded from further analysis. The mean birth weight of the 454 Group O patients was 3245 gm.; that of the 76 Group D patients, 2392 gm. The difference in birth weight between the two groups was highly significant (Figs. 1 and 2).*

Inspection of the group with D manifestations revealed that there were 42 patients with one or more of those designated as C. Of these 42 patients, 18 had convulsive seizures; 36, mental deficiency; 5, athetotic or ataxic movements; 11, positive tonic neck reactions; 7, greater impairment of upper than of lower extremity function; 19, definite asymmetry of extremity function, and 10, hypotonic musculature. All but one patient had two or more C manifestations, and in this instance there were obvious athetotic movements. Within the D group there were 34 patients lacking any of the C manifestations, and these constituted the D+S subgroup. The mean birth weight of the D+C subgroup was 2983 gm. (Fig. 3); that of the D+S subgroup, 1662 gm. (Fig. 4). Comparison revealed that the birth weights were significantly lower in the D+S than in the D+C subgroup.† To determine whether the D+C and the D+S subgroups differed from the O group in regard to birth weight, both subgroups were compared with the O group. This comparison revealed a highly significant difference between the D+S subgroup and

* Comparison of the distribution of the individual birth weights grouped at increments of 10 oz. in the two groups of cases, D and O, by the analysis of variance technique, where the variance ratio, F="between" mean square/"within" mean square, gives the following result: $F=85.4$; $n_1=1$; $n_2=528$. From this, P is of the order of magnitude of 3×10^{-20}.

† Comparison of the distribution of the individual birth weights grouped at increments of 10 oz. in the two subgroups, D+S and D+C, by analysis of variance gives the following result: $F=713$; $n_1=1$; $n_2=74$. From this, P is of the order of magnitude of 1×10^{-16}.

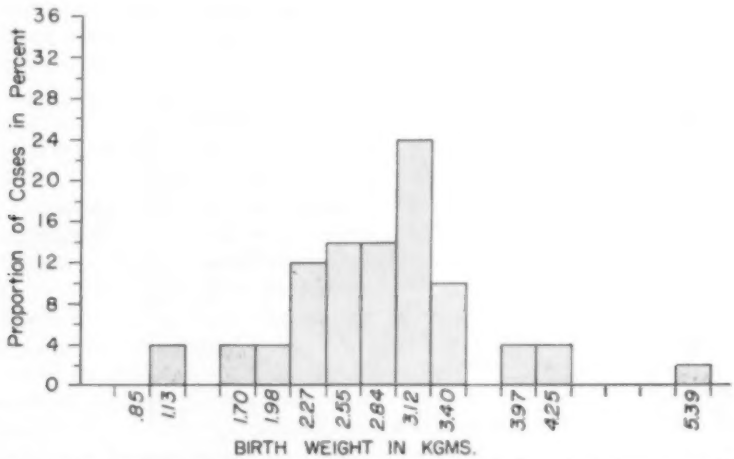

Fig. 3.—Birth weights of 42 Group D+C cases. These patients had signs conventionally identified with bilateral corticospinal (pyramidal) tract damage and in addition had signs referable to other regions of the brain. Mean birth weight 2983 gm. (6 lb. 9 oz.).

the O group,‡ but none between the D+C and the O groups.§

In addition to the major difference of birth weight between the D+C and the D+S subgroups, abnormalities of delivery were known to have occurred in 22 of the 42 D+C patients but in only 8 of the D+S patients (Fig. 5). These abnormalities fell into the following categories: D+C subgroup—prolonged labor, six; breech delivery, three; multiple birth, one; face presentation, one; transverse lie, two; abruptio placenta or placenta praevia, four; cesarean section, three, and eclampsia, one;

‡ Comparison of the D+S subgroup with the O group by means of analysis of variance gives the following result: $F=170.1$; $\nu_1=1$; $\nu_2=486$. P is less than 10^{-20}.

§ Comparison of the D+C subgroup with the O group by analysis of variance gives the following result: $F=4.7$; $\nu_1=1$; $\nu_2=496$. $P\sim0.1$.

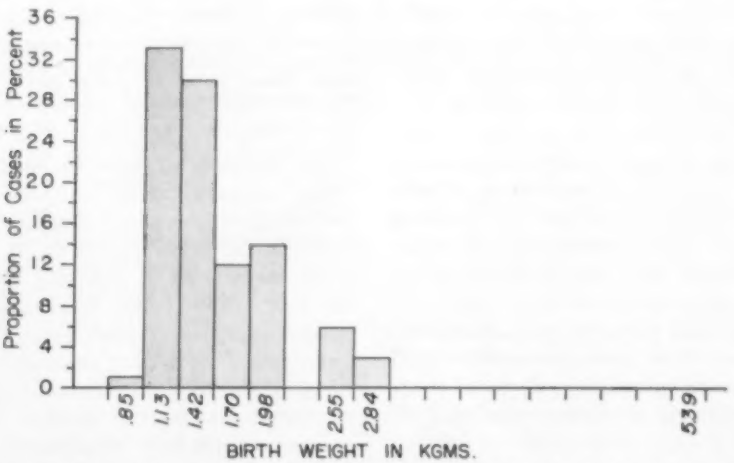

Fig. 4.—Birth weights of 34 Group D+S cases. These patients had signs conventionally identified with bilateral corticospinal (pyramidal) tract damage only, the lower extremities being principally involved. Mean birth weight 1662 gm. (3 lb. 10 oz.).

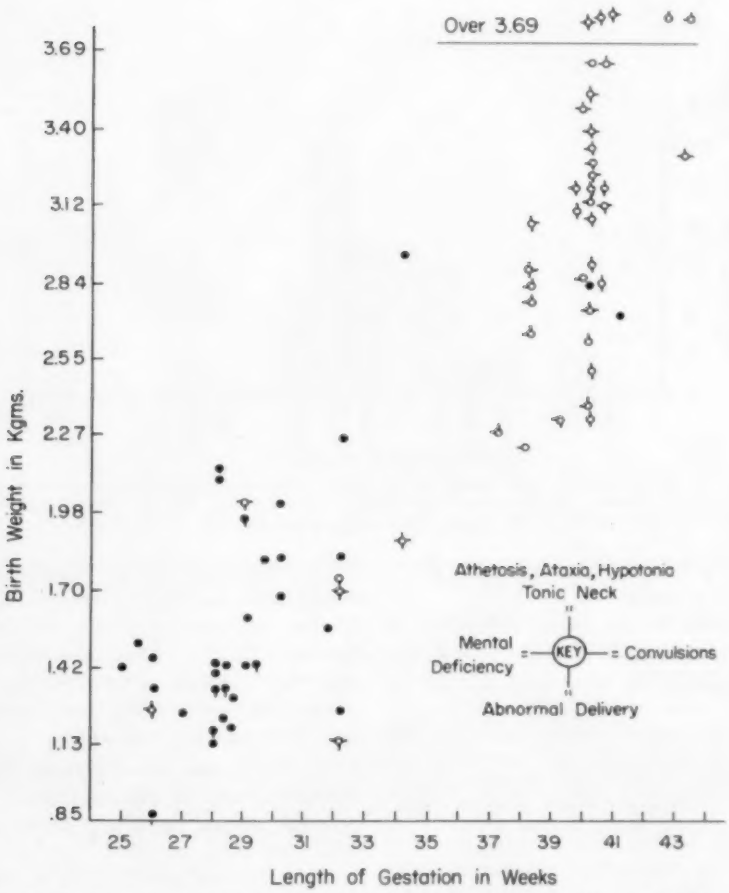

Fig. 5.—Scattergram of Group D cases (Little's disease). Birth weight on ordinate, gestation time on abscissa. Whiskers represent manifestations of individual patients, as designated in key. Solid dots represent D+S patients (simple spastic diplegia); hollow dots, D+C patients (complex diplegia). Level of prematurity equaled birth weight of 2272 gm. (5 lb.) or 2500 gm. (5 lb. 8 oz.).

one patient in this group was known to have had intracranial hemorrhage at birth. D+S subgroup—prolonged but intermittent labor, two; breech delivery, three; multiple birth, one, and cesarean section, one. Comparison of the D+C and D+S subgroups with respect to the abnormalities of delivery cited above revealed a significantly greater association of these abnormalities with the D+C than with the D+S subgroup.‖

The incidence of bleeding during pregnancy, excluding those instances of late hemorrhage due to placental separation, was higher in the D+S than in the D+C subgroup, there being 15 instances in the former and 7 in the latter. Information about possible asphyxia at birth, in the form of statements about delayed onset of crying or breathing or the administration of artificial respiration, was available in 29 of the D+C patients, of which 19 were known to have

‖ Comparison of the D+C and the D+S subgroups in regard to the occurrence of abnormal factors of delivery by the χ^2-method gives the following result: $\chi^2=8.05$; $\nu=1$, whence $P\sim0.005$.

responded poorly, and in 25 of the D+S patients, of which 9 were known to have responded poorly.

Further differences were found between the D+S and D+C subgroups. EEG's obtained in 21 of the D+C patients were found to be distinctly abnormal in 17 instances, while none of 13 EEG's obtained in D+S patients was judged to be abnormal. Hypoplasia of tooth enamel was found in 8 of 14 D+C patients, the position of the lesions indicating a disturbance of enamel formation occurring around the ninth month of gestation in 4, earlier in the remaining patients.[18] Such hypoplasia was found in 15 of 18 D+S patients, the position of the enamel lesions in all instances indicating a disturbance of enamel formation between the fifth and seventh months of gestation, this time in most patients correlating with that of the premature birth.

In the D+S subgroup there were only three patients who had birth weights over 2500 gm. One of these was born at the 34th week of gestation, of a mother with severe diabetes. Infants born of diabetic mothers are often heavier than others of equal gestational age. In the D+C subgroup were six patients with birth weights under 2500 gm. Two of these children had hemiplegia in addition to D manifestations (one of them, in addition, had a porencephalic cyst in one hemisphere). The possibility that these patients had two separate disorders was considered but could not be proved. Of the other four patients, one was born microcephalic, one was delivered by cesarean section for abruptio placenta, one was born following prolonged labor and had asphyxia neonatorum, and in one instance the mother was in eclamptic convulsions at the time of delivery.

Comment

From an analysis of this clinical material it can be concluded that patients with so-called Little's disease can be segregated into two separate entities, or taxa, which may be designated as simple spastic diplegia on the one hand and complex diplegia on the other. Simple spastic diplegia exhibits symptoms and signs customarily interpreted in terms of damage to the corticospinal or pyramidal tracts, while complex diplegia exhibits, in addition, symptoms and signs usually interpreted in terms of dysfunction of other portions of the brain. Simple spastic diplegia has been found to correlate very significantly with low birth weight, to such an extent as to indicate a causal, though not necessarily direct, relationship between prematurity and this disease. Complex diplegia, on the other hand, exhibits no significant correlation with low birth weight.

Brissaud,[14] writing in 1894, believed that prematurity itself was the cause of simple spastic diplegia, myelinization of the pyramidal tracts being delayed by the premature birth. Freud,[4] however, pointing out that not all premature infants develop this disease, proposed that premature birth in these infants was a result of a disease process responsible for both prematurity and Little's disease. Latham, Anderson, and Eastman[19] and also Eastman and DeLeon[20] suggested that uterine bleeding during pregnancy might be causally related to both prematurity and Little's disease. However, in the present study, such bleeding occurred in less than half the mothers and would not appear to be a direct factor.

Collier[3] developed the concept that the type of neurological picture resulting from any of a variety of disease processes depended upon the time of occurrence of the insult during the development of the nervous system. Since more rapid changes occur in the developing nervous system during the earlier months than during the later months of gestation, one might anticipate considerable variability in the symptoms and signs observed in the prematurely born infant, particularly since prematurity covers a wide time span. However, diversity of symptoms and signs was not a conspicuous feature of prematurely

born patients in the present study, the findings being relatively uniform. On the other hand, patients born at term, and exhibiting so-called Little's disease, revealed a considerably wider diversity of neural manifestations.

Childs and Evans [21] studied the relationship of birth weight to Little's disease and found a distribution curve very similar to that presented here. They commented upon the bimodal character of the curve and considered—only to reject—the possibility that there might be two forms of the disease, one correlating with low birth weight, the other not. It seems probable that they were unable to accomplish an effective separation of their cases, since these were segregated on the basis of presence or absence of upper extremity involvement. This might have resulted in a division of their cases of simple spastic diplegia, as here considered, into two categories, mild and severe. Many investigators [22] have proposed that brain damage from anoxia or asphyxia might be a principal cause of the symptoms and signs seen in Little's disease and in cerebral palsy in general. Unfortunately, the present data offer no contribution to this aspect of the problem, and an extended discussion of the pertinent literature would be beyond the scope of this paper. However, one might propose this query: Why does simple spastic diplegia correlate so significantly with prematurity, and complex diplegia not?

Summary

A study of 76 patients with Little's disease revealed that they could be segregated into two groups having relatively distinct clinical characteristics. One group, called simple spastic diplegia, was found to be composed of persons who, for the most part, had had low birth weights. In sharp contrast, low birth weight was not a prominent feature of the other group, which was called complex diplegia. The significance of low birth weight (prematurity) in the pathogenesis of simple spastic diplegia is discussed.

Jack Guyton, M.D. assisted in the statistical treatment of the data.

Henry Ford Hospital (2).

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The Determination of Genetic Sex in Children

A Critical Evaluation of the Reliability of Polymorphonuclear Leukocyte Morphology

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Until relatively recently no practical method was available for the determination of the genetic sex of an individual. However, in 1949, Barr et al.[1] described an extranucleolar chromatin mass or "satellite" as a histologic characteristic of the nervous system cells of female cats. Five years later Emery et al.[2] reported that in the cells of the epidermis of living human subjects an extranucleolar chromatin mass was seen in greater than 25% of the cells in females and in less than 10% of the cells in males. A few months later Davidson et al.[3] reported the presence of an extranuclear chromatin mass, or "drumstick," in the polymorphonuclear leukocytes of human females. With these advances came the opportunity for the early and accurate diagnosis of genetic sex in patients in which an abnormality in formation of the genital system had occurred.

The demonstration of hormone dysfunctions in a variety of clinical syndromes (adrenogenital, Turner's, Kleinfelter's, and others) has increased the importance of establishing the genetic sex of certain patients. In such patients genetic sex determination is useful both as a diagnostic aid and as a research tool.

The present study was undertaken to evaluate critically the reliability and practicability of the determination of genetic sex, in infants and children, on the basis of polymorphonuclear leukocyte morphology.

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Methods and Materials

Sixty-five patients, ranging in age from 4 weeks to 75 years, were included in a blind study. Several sets of slides were resubmitted to examination as a further check on reliability. The blood films were prepared from a finger stick, with care being taken to obtain a large film with a definite feather edge. The films were stained with Wright's stain for two minutes, buffered with distilled water for six to seven minutes, washed with water, and dried in air. After the entire blood film was covered with immersion oil, scanning with the high dry lens (×40) was started at the feather edge. When a suspicious polymorphonuclear leukocyte was encountered it was observed in greater detail, with use of the oil-immersion lens (×90). Although it was possible, at times, to distinguish the female chromatin mass with high dry or even low magnification, this was always confirmed by observation under oil immersion. Only the feather edge and the adjacent few millimeters of the blood films were found to be satisfactory for good morphologic study.

Results

Among the 65 patients studied 5 errors were made, giving a percentage of 92.3% correct interpretations. Two of the errors were considered to be due to faulty technique, and one error was thought to be the result of inexperience. One of the other incorrect interpretations later was resubmitted and interpreted correctly, leaving only one patient who, for undetermined reasons, was incorrectly interpreted. When the three determinations that were incorrectly read because of the poor quality of the blood films were eliminated, the percent of correct interpretations was 96.7.

A comparison between the first 35 patients studied and the last 30 patients studied revealed that all five of the errors were made during the first half of the study, giving a percentage of correct interpretations in the last half of the study of 100%. We are inclined to attribute this to the experience gained during the first half of the study.

In this study observation of an average of three slides per patient was necessary for interpretation, with a minimum of one slide and a maximum of six slides. The average time required for interpretation was 75 minutes, with a range of 15 minutes to 3½ hours. The extremes just mentioned presented an interesting situation inasmuch as the interpretation which required only 15 minutes was on an adult female in which the chromatin mass, characteristic of a female, was found in 13 of 124 polymorphonuclear leukocytes observed while the interpretation that required 3½ hours was on an 8-year-old female pseudohermaphrodite in which only 6 diagnostic cells were found in 965 polymorphonuclear leukocytes counted.

During the study it was noted that typical drumsticks were occasionally observed on eosinophils. This was observed only on females and may constitute an additional finding not previously described.

Comment

The data presented appear to demonstrate that in the hands of an experienced observer this method of genetic sex determination is very accurate. This raises the question of practicability of application. The interpretations in this study were made by a self-trained senior medical student who was guided on matters of approach to the study and selection of case material only. The morphologic interpretations were made by him without advice or assistance. This would indicate that the determination of genetic sex by means of polymorphonuclear leukocyte morphology is both practical and accurate and requires no more total time than other methods such as skin biopsy or buccal mucosal smear. The relative lymphocytosis of children offered the only disadvantage encountered in our study. Because of this, polymorphonuclear leukocytes were less numerous than in adults and more time was required for interpretation.

In our study one morphologically *perfect* drumstick was sufficient to make the diagnosis of genetic female, since no perfect chromatin mass was seen in a male in this series. It is hoped that this observation can be corroborated or refuted, since it varies somewhat from the accepted criterion of 6 such cells per 500 polymorphonuclear leukocytes. In support of this observation were the findings on the patient with the adrenogenital syndrome. Although 965 polymorphonuclear leukocytes were observed before 6 diagnostic cells were found, 2 of these 6 cells were considered to be *perfect*.

The two sources of error in our study were technically poor slides and morphologic artifacts. Inadequate blood films should be discarded, and new preparations should be made. Morphologic artifacts included additional nuclear lobes or "pseudodrumstick," in which two filamentous connections can be visualized; an indistinct cell boundary; a platelet superimposed in ideal position but without a filamentous connection, and the presence of masses known as "clubs" that are correctly located and have a filamentous connection but which are much smaller than drumsticks. We found it advantageous to examine more than one slide since, for unknown reasons, more diagnostic cells may be present on one slide than another.

In view of the results of the study reported in this paper and of the experience of others with the various methods known to be reliable for the determination of genetic sex,[8] it would seem that the morphologic study of either peripheral blood films or mucosal smears offers the most convenient means of determining genetic sex.

Both techniques are simple, nonsurgical, easily repeated, accurate in skilled hands, and little or no trouble to the patient. We feel that the choice between these two methods is arbitrary.

Summary

The morphology of the polymorphonuclear leukocytes of 65 patients of both sexes, ranging in age from 4 weeks to 75 years, was studied in a blind fashion to evaluate critically this method of genetic sex determination.

Five errors were made in the entire series, giving an over-all percentage of correct diagnosis of 92.3%.

All of the errors in diagnosis were made during the first half of the study. Three of the errors were believed to have been caused by poor technique in preparing slides, and, since later in the study no attempt was made to read poorly prepared films, it is probable that these three errors could have been avoided.

The results of this study indicate that, under the proper circumstances, the morphology of the polymorphonuclear leukocyte is a reliable indicator of genetic sex.

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Primary Interstitial Myocarditis

Report of an Epidemic Outbreak

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The acute isolated interstitial (Fiedler's) myocarditis is a well-known clinical and pathological entity. It was first described by Fiedler in 1899 in an adult; later, by Zuppinger and by Forster in children,[1] and since then a great number of case reports have appeared in the literature. This type of interstitial myocarditis should be diagnosed only in the absence of any other pathological conditions that might be correlated with the myocardial involvement.[2,3] The cause of this disease has never been clearly understood. Many theories have been proposed, and an infectious origin has also been considered possible.[4,5] However, epidemic outbreaks of interstitial myocarditis have only recently been described.

The first report of an epidemic outbreak came from Munich, Germany, where 140 cases of interstitial myocarditis in infants were observed during the years 1937-1944.[6,7] The epidemiological pattern was believed by the author to suggest an epidemic due to a living agent (virus). The infants were 1 month to 2 years old, and all, except one, died with a clinical picture of acute heart failure.

From South Africa came a report [8] of an outbreak of interstitial myocarditis in a maternity home in Johannesburg in September and October, 1952. Of 10 infants, aged 5 to 17 days, 6 died, and interstitial myocarditis was found at the postmortem examination. In 1954 a similar outbreak was observed in a maternity home in Southern Rhodesia.[9] At the time of both outbreaks, an epidemic of Bornholm disease was prevalent in the corresponding regions.

In 1955, during an epidemic of "summer grippe" in Amsterdam, four cases of myocarditis were observed in newborn infants and all died.[10,11] In these three outbreaks, in Johannesburg, in Southern Rhodesia, as well as in Amsterdam, Coxsackie virus was obtained from the stool and from autopsy material and was considered to be the etiological agent.

Eight cases of interstitial myocarditis were observed in Athens [12] in 1955 in a relatively short period of time. It was, therefore, believed by the authors that this large number of cases may represent an epidemic outbreak of this disease.

The purpose of this paper is to describe an outbreak of interstitial myocarditis in infants and children in the Haifa area, Israel. In the time between March, 1956, and December, 1957, a total of 57 cases of interstitial myocarditis were observed and 50 of the patients died. This represents a particularly marked increase in the morbidity rate of this disease, in comparison with the previous years.

Clinical Picture

The majority of the infants reported in this series followed a remarkably similar clinical course. A few days before the onset of the acute heart failure a general malaise was noted, often accompanied by an upper respiratory tract infection. This prodromal stage lasted usually 1 to 3 days, but in several cases it could be traced back as far as 10 days and even more. Most

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of these infants had been examined by physicians at this stage, but except for a mild respiratory infection nothing abnormal was found. The symptoms and signs of acute heart failure appeared suddenly. The child became restless and dyspneic and rejected food. The physical examination revealed a restless child with a marked pallor of the face and cyanosis of the lips. The breathing was labored, with a retraction of the costal arch. The extremities were cold and livid. The liver was markedly enlarged and palpable 5 to 8 cm. below the costal margin. The heart sounds were usually weak, and no murmurs were present. The pulse rate was always over 150 per minute, often up to 200. Moist rales were heard on auscultation of the lungs. The body temperature was usually normal or slightly elevated. The physical development of nearly all children was good or excellent, and the body weight of the majority of them was in the higher percentile group.

In spite of treatment with digitalis, cortisone or prednisone, mercurial diuretics, antibiotics, oxygen, chlorpromazine (Largactil), and γ-globulin, no improvement in their condition was observed. The dyspnea was progressive, and the general condition deteriorated dramatically. The child became comatose and died usually in less than 24 hours after the first signs of the acute heart failure.

In 15 infants the deterioration was so rapid that they died before reaching the hospital. The diagnosis was made by post mortem examination. The signs and course as related by the attending physician, parents, or both were the same as those of the infants and children seen by us.

The prodromal stage was not always elicited in the history. In some cases the disease appeared suddenly, without any previous symptoms. On the other hand, in several infants and children the course of the disease was somewhat slower. Their general condition deteriorated within a few days; the clinical signs of heart failure were less severe at the beginning of the disease, but the course was progressive, and they died with the same signs and symptoms of acute heart failure.

Seven children recovered from this disease and survived. The diagnosis was made in these cases by clinical and laboratory means (x-ray, ECG). The clinical picture was the same as in other cases where the outcome was fatal. The onset of the heart failure was sudden, usually after a prodromal stage. The heart failure was severe; the infants were cyanotic, dyspneic, pale, and restless. The liver was enlarged; the lungs were full of rales, and the tachycardia was extreme. These patients received the same treatment as did those who succumbed the disease, but the general condition of the children who survived improved clinically after one or two days. A few days after the onset of the acute heart failure they showed no clinical signs of a severe disease.

At the follow-up examination these infants and children were in good general condition, with a normal development. A soft systolic murmur was heard over the precordium in most cases, but no other pathological findings were present. The heart murmur was usually noted for the first time some days after the improvement of the child's condition.

Five of the children recovered from the acute heart failure but developed a second attack with the same clinical picture, and two of these had a third attack. The recurrences occurred usually three to five weeks after the first attack, and their onsets were always as sudden as the first time. Between the attacks the children were in good general condition. From this group of five infants and children, two recovered completely and survived, one of them after two attacks and one, after three. They were repeatedly examined for more than 10 months and were in good general condition. Of the remaining three children two died at the second recurrence and one died at the third attack, which occurred during a varicella infection.

To this group of 57 cases of interstitial myocarditis a small group of cases may be

added in which the diagnosis of myocarditis could not be made conclusively. They showed a clinical picture which was similar to the cases reported in this series but to a somewhat milder degree. The x-ray examination and the ECG did not confirm the diagnosis of myocarditis, but there were several features resembling the reported cases. The patients all recovered from the acute disease and remained well. These cases may have represented a mild form of the disease described in this report. The evidence that these patients suffered from interstitial myocarditis was not convincing, and they were, therefore, not included in the present report.

Laboratory Findings

Most of the children died a few hours after admission to the hospital, and laboratory examination could not be performed in all cases.

Blood Examinations.—The hemoglobin values were low in most cases. Examinations were performed in 17 infants and ranged from 7.0 to 10.8 gm. per 100 ml., with a mean value of 9.1 gm. per 100 ml. It has, however, to be stressed that low hemoglobin values are common findings in infants in this country. The white blood cell count was performed in 15 children and showed a range from 6200 to 25,000, but in the majority it was less than 11,000. The differential count was within normal limits in all cases. The total proteins and albumin-globulin ratio were normal in five cases; the antistreptolysin titer was normal in three cases, and C-reactive protein was negative in three cases. The sedimentation rate, taken in seven cases, was always slow.

X-Ray Appearances.—In 25 cases x-ray examinations were performed in the x-ray department of the Rambam Government Hospital, Haifa. The x-ray examination showed an enlargement of the cardiac shadow in all cases. In the majority of the examined patients the dilatation of the heart was very marked, but the individual parts of the heart were still distinguishable. In a few cases the heart dilatation was particularly severe; in these cases the differentiation of the individual heart segments was no longer possible, the x-ray appearance resembling that of pericarditis. In all patients there were clear signs of pulmonary congestion of varying degrees. All cases showed signs of pleural fluid along the thoracic wall, in the interlobar fissure or in both. In most of the cases weak heart pulsations were noted on screening. In the children who recovered, the x-ray findings were the same during the acute stage of the disease; with the clinical recovery the heart shadow gradually decreased in size, and in a few of the cases the heart was found to be normal on reexamination after several months. Detailed report of the x-ray observation will be published.[13]

Electrocardiographic Findings.—Electrocardiographic examinations were done in 21 cases, and in all of them the records were nearly identical. Sinus tachycardia was invariably present, with a pulse rate of over 150 per minute. The T waves were flat or negative in most leads, and the ST segment was below the isoelectric line. In the majority of cases the QRS complex was very low. The infants who recovered and survived had the same electrocardiographic findings during the acute stage of the disease, and repeated examinations after the clinical recovery showed constant improvement and complete normalization of the electrocardiogram.

Viral Studies.—Autopsy material of 26 cases was sent for viral examination. Organ suspensions (heart, brain, spleen, lung, etc.) were injected into suckling and adult mice, and all these mice failed to reveal any signs of a disease. They were killed at various times, and organ suspensions were injected into new mice. Three to four such passages were performed, but no pathological signs were noted in these animals. The organs of these mice were examined, but no pathological findings were discovered.

Blood and organ suspensions from the infants dying of interstitial myocarditis

were cultured on tissue (placenta or monkey kidney). In one single case a virus was isolated from the heart but not from other tissues from the same case. This virus has not yet been identified, owing to technical difficulties. In all other 25 cases no growth of viruses was obtained.

Autopsy Findings.—In 49 of 50 children who died a complete autopsy was performed. The pathological findings were remarkably uniform. The striking feature was the dilated and thickened heart, which weighed 70 to 100 gm., according to the age (normal, 30 to 70 gm.). The whole heart was uniformly dilated. In several cases there was a clear yellowish fluid accumulation in the pericardial sac (50 to 100 cc., approximately), but no signs of inflammation were present. The epicardial surface of the heart was purplish. The myocardium was pale, with a "cooked" appearance. The internal part of the myocardium was somewhat paler than the outer part. The heart wall was thickened throughout. The valves showed no abnormalities, and no congenital heart defects were found in any of the cases. The endocardium was smooth and shining, but in less than half the cases a subaortic whitish thickening of the endocardium was noted, in few cases resembling frank fibroelastosis.

The lungs were edematous and congested, and in half of the cases bilateral hydrothorax was present, with 100 to 250 cc. of clear yellowish fluid in each side. The internal organs were acutely congested. The brain and spinal cord were macroscopically normal.

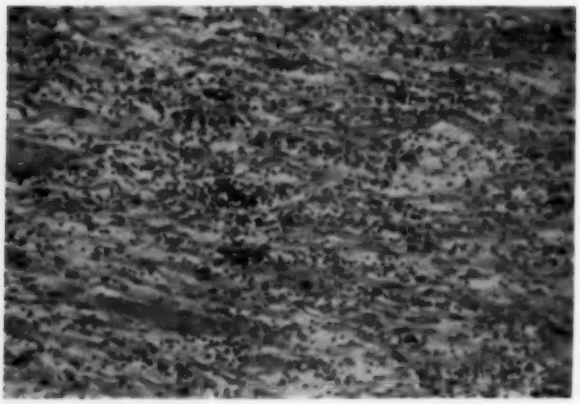

Fig. 1.—Microscopic picture of the heart muscle. Marked interstitial round-cell infiltration.

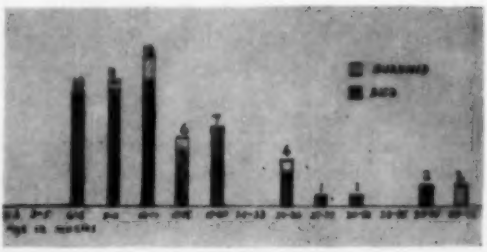

Fig. 2.—Ages of infants and children.

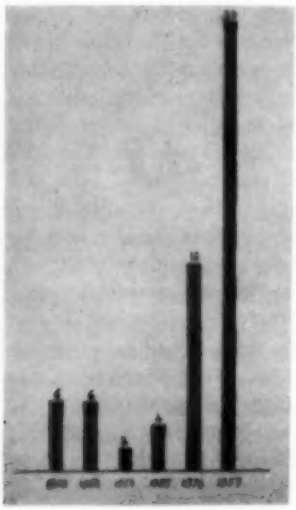

Figure 3

Fig. 3.—Number of cases of primary interstitial myocarditis in the Haifa area, 1952-1957.

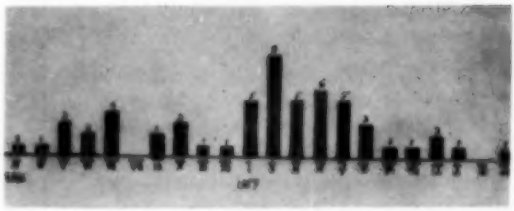

Figure 4

Fig. 4.—Number of cases of primary interstitial myocarditis between March, 1956, and December, 1957.

The microscopic examination of the myocardium revealed a marked interstitial infiltration with small round lymphocyte-like cells, usually diffused; sometimes patchy, with no relation to blood vessels, and more pronounced toward the epicardial surface (Fig. 1). Patchy degenerative changes of cardiac muscle were often seen. The thickening of the myocardium was due to this infiltration, and no true hypertrophy of muscle fibers was noted. In nearly half of the cases there was a mild round-cell infiltration of the epicard. The endocard was thickened by a mild proliferation of both elastic and collagen fibers in more than 50% of the cases, sometimes with a slight round-cell infiltration.

The lungs were in all cases congested and edematous, and in the alveoli of many lungs large "heart failure"-like cells were found. Patchy areas of alveolar walls thickened by lymphocytic infiltration were found in several cases. In all other internal organs (including brain and spinal cord) only congestion was found.

In some cases the examined striated muscle (diaphragm, psoas, and gastrocnemius) showed slight patchy interstitial lymphocytic aggregation. These changes were not seen in all cases.

Statistical and Epidemiological Data.—All 57 cases reported in this series were in the age group between 6 months and 3½ years. Contrary to some previously reported outbreaks, where all cases occurred in newborn infants,[8-11] we have not observed one single infant younger than 6 months. More than two-thirds of the patients were between 6 and 18 months of age (Fig. 2).

There was a slight, not statistically significant, predominance of girls in our series (31 girls to 26 boys). A high preponderance of girls was noted in the series by Choremis et al. (7:1).[12]

The marked increase of the incidence of interstitial myocarditis is shown in Figures 3 and 4. The rise began slowly during the year 1956, when 18 cases occurred, which represents a significant increase in comparison with the previous years (1952, six cases; 1953, six cases; 1954, two cases, and 1955, four cases) (Fig. 3). The incidence rose sharply during the first months of the year 1957. The number of cases in this year was 39. The peak of incidence was in February, with nine cases. The number of

cases decreased in the following months, and only 6 cases of interstitial myocarditis were seen in the second half of the year 1957 (Fig. 4).

There was no marked increase in the incidence of primary interstitial myocarditis in any other part of this country. In all other hospitals in Israel only sporadic cases were observed, and their number was not significantly greater than the number of cases with primary interstitial myocarditis during the previous years.

All the infants and children reported in this series were from the Haifa area. Most were from rural districts. There was evidence of some localized concentrations of cases. In a few, rather small places several cases of myocarditis occurred. Furthermore, in several places most of the cases appeared within a relatively short time.

At the time of this outbreak of primary interstitial myocarditis no other epidemic disease was noted in this area either among adults or among children. This disease was never seen twice in one family or in the immediate neighborhood. We had no knowledge of any other disease in the siblings or parents of the affected cases, either at the time the child was brought to the hospital or prior to this. Two infants came from separate baby-homes, where no other diseases were noted at this time. It was particularly noted that the greatest majority of the infants reported in this series were in good or excellent nutritional state.

The distribution of cases between the Jewish and Arabic population of Israel was not greatly different from their proportion in the population in this area. There were 4 Arabic and 53 Jewish children.

A detailed epidemiologic study of this outbreak is in progress.

Comment

The marked increase in the incidence of interstitial myocarditis in our area, as recorded in Figures 3 and 4, appears to be of clear statistical significance and to support the assumption of an epidemic outbreak of this disease. There may not be any question of an unawareness of this disease prior to this outbreak, as complete postmortem examinations are performed in more than 90% of all children dying in the hospitals in this area, as well as in other hospitals in this country, especially of all children who die suddenly. Furthermore, it has to be stressed that this outbreak was noted in one part of this country only and that there was no increase of this disease in any other part of Israel.

The diagnosis was made during life by the clinical picture of acute heart failure and by x-ray and ECG examination, and in the children who died the diagnosis was proved by postmortem findings. The clinical characteristic was the sudden onset of acute heart failure in a previously normal and healthy-looking child, with extreme restlessness, tachycardia, pallor, and enlarged liver. The ECG showed typical findings of myocardial damage. The x-ray was a useful diagnostic tool, usually showing an extremely enlarged heart shadow, signs of congestion in the pulmonary circulation, pleural effusion, and weak heart pulsation.

The treatment was not uniform in all cases in our series, but nearly all drugs recommended were prescribed. Steroids were given to the majority of patients who were admitted to the hospital. These drugs have been recommended in the treatment of this disease,[14] but we have not been able to observe the therapeutic properties of the steroids in our series of patients. Digitalis was given to every child admitted to the hospital. Various dosages were tried, without any difference in the outcome. Mercurials did not show clinical effects. Antibiotics were given in most cases, and chlorpromazine, γ-globulin, and acetazolamide (Diamox) were tried for several patients, with no beneficial result. It has to be pointed out that the seven children who survived and the three others who recovered from the first attack, but died subsequently, received the same treatment as most of the other patients.

The etiology of this disease is not yet established. Some cases of interstitial myocarditis reported in the literature were found to be connected with viral infections. Helvig and Schmidt [15] and Schmidt [16] obtained a virus from chimpanzees which died of interstitial myocarditis. This virus produced myocarditis and encephalitis in a series of mice, hamsters, and guinea pigs. The virus was later identified as the "encephalomyocarditis virus." It has also been isolated from children suffering from various cerebrospinal diseases, but no case of myocarditis in man has yet been definitely attributed to this agent.[17] Coxsackie virus was found associated with interstitial myocarditis [8-11,18,19] and was believed to be the etiological agent in those cases.

In our series of cases viral studies did not reveal the etiological agent. In one single case a virus was obtained from the heart muscle only. Unfortunately, this virus has not yet been identified, because of technical difficulties. In all the other 25 cases, in which viral studies were performed, no growth of any virus was obtained. It may be concluded that Coxsackie virus, as well as encephalomyocarditis virus or similar viruses, was not present in the organs of these 25 cases, and it seems, therefore, probable that these viruses were not the etiological agents of primary interstitial myocarditis in the cases which occurred during this outbreak.

The epidemiological pattern of this outbreak may support the assumption of an epidemic due to a living agent. Most of the cases were geographically and chronologically aggregated, mostly in rural settlements. Furthermore, the age distribution of the patients (from 6 months to 3½ years, with the peak at 1 year) corresponds to the ages when many infectious diseases appear, because of the lowest values of natural immunity at this age. However, no connection with any infectious disease was noted, nor were we able to recover the causative agent in our series of cases.

Summary

Fifty-seven cases of primary interstitial myocarditis were observed in the Haifa area, Israel, during the period from March, 1956, to October, 1957. This represents a marked increase in the morbidity rate of this disease. Fifty children (87.7%) died.

All the patients were in the age group between 6 months and 3½ years, and most of them were in excellent nutritional state.

The onset of the disease was sudden, often after a prodromal stage of a mild respiratory infection, and led to death usually after less than 24 hours. The clinical signs and the electrocardiographic and x-ray findings were typical of acute heart failure. The postmortem examination showed a uniformly dilated heart with marked interstitial infiltration with small lymphocyte-like cells. Seven children recovered and survived; five children recovered from the acute heart failure but developed another attack. Various drugs were tried without any result.

covered and survived; five children recovered from the acute heart failure but developed another attack. Various drugs were tried without any result.

Virological studies were performed in nearly half of the cases. In one single case a virus was grown on monkey kidney tissue culture from the heart muscle but not from other organs from the same patient. In all other cases no virus was recovered from the autopsy material.

The epidemiological pattern, the geographical and chronological distribution of the cases, and the age incidence suggest an epidemic outbreak of primary interstitial myocarditis.

Drs. B. Gellei and B. Griffel, from the Department of Pathology, Rambam Government Hospital, Haifa, made the description of the autopsy findings, and Dr. J. Munk, Head of the X-Ray Department and Dr. J. Heichmann, Head of Medical Department A, analyzed the x-ray and ECG findings. Dr. N. Goldblum, Head of the Virus Laboratory, Ministry of Health, Tel-Aviv, and Dr. E. Eylan, Head of the A. Felix Laboratories for Public Health, Tel-Aviv, performed the virological studies. Dr. B. Ostrowsky, Head of the Department of Pediatrics of the Rothschild Municipal Hospital,

Haifa, gave permission to include the cases from his department in this study.

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Sickle-Cell Anemia in Infancy

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Sickling can be produced in the blood of young Negro babies with sickle-cell trait. The percentage of cells showing this change is low but will increase as the infant matures. The homozygous state is present from birth; however, recognition of the symptomatic condition is rare in infants under the age of 4 months. Investigation of the literature reveals only four case reports in infants less than 3 months of age. These cases predate the period when electrophoretic and biochemical procedures could be applied. This article concerns case reports of two infants with sickle-cell anemia who were studied with these methods.

Methods

The erythrocyte and leukocyte counts were made by routine methods. Hemoglobin was determined as cyanmethemoglobin with a Klett-Summerson photoelectric colorimeter.[1] The hematocrit values were determined by the Wintrobe method. Tests for sickling were performed by the sealed cover-slip method, with use of sodium metabisulfite as a reducing agent. The reticulocyte counts were done with use of brilliant cresyl blue dye, the cells being counted on the dry smears, which had been counter-stained with Wright's stain.

Paper electrophoresis was by the method described by Smith and Conley,[2] with modification. Barbital (Veronal) buffer was used at pH 8.6 and an ionic strength of 0.06 at 360 volts for three and one-half to four hours.

Moving-boundary electrophoresis was also done on the hemolysate. The run was performed with use of a cacodylate buffer at pH 6.5 for seven hours at 20 ma.[3]*

Alkali denaturation was performed on hemoglobin solutions by the method of Singer et al.[4]

Radioactive erythrocyte-survival studies were performed by incubating the patient's erythrocytes with radiochromium and reinjecting them into the patient's blood. Serial samples for radioactive counts after recirculation were then taken, and counts were made in a well scintillation counter.[5]

An Ashby survival test was done, with use of a potent liquid antiserum.[6] Unagglutinated counts of less than 50,000 were obtained on blank specimens.

Report of Cases

CASE 1.—A 24-day-old Negro boy was well until the day prior to his admission to the hospital, when his mother noted irritability, scleral icterus, and dark urine.

The mother had had an uneventful pregnancy of nine months' duration, and the delivery was normal. The infant's birth weight was 7 lb. 11 oz., and he was fed an evaporated milk formula which was well tolerated. A sibling, one year of age, was known to have sickle-cell anemia.

He was a fairly well-developed and well-nourished Negro boy, with marked scleral icterus and a greenish-yellow tinge to the skin. His weight was 8 lb. 8 oz., and his temperature, 99.8 F. The liver was palpable 6.0 cm. and the spleen, 4.0 cm. below the costal margins. Examination of the heart and lungs revealed no abnormalities.

Laboratory Examinations.—Urinalysis: Trace of albumin; bile was consistently present, and urobilinogen varied from negative to slight trace in the several specimens taken. Stool examination: A trace of urobilinogen was present. Blood (Table 1): red blood cells, 2,600,000 per cubic millimeter; hemoglobin, 7.0 gm. %; platelets, 416,000 per cubic millimeter; reticulocytes, 6.8%. White blood cells, 20,500 per cubic millimeter. Differential count: segmented neutrophils, 31%; band-form neutrophils, 3%; eosinophils, 1%; monocytes, 9%; lymphocytes, 56%. There were 137 nucleated red

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* Mrs. Lily Singer, of the Department of Hematologic Research, The University of Chicago, performed the Tiselius electrophoresis.

TABLE 1.—*Hematologic Values of the Family of Patient 1*

Subject	RBC	Hb.	VPC	MCV, Cu. μ	MCHC, %	Sickle Prep.	Stained Smear		Reticulocytes, %	Hemoglobin by Paper Electrophoresis
							Targets	Sickling		
Patient	2.4	8.1	24	100	33.8	Pos. (100%)	4+	4+	6.8	S+F
Mother	4.2	12.5	38	90.5	32.8	Pos.	0	0		A+S
Father	4.4	13.8	41	93.1	33	Pos.	4+	±	1.1	S+C
Brother	2.7	6.4	21	77.8	30.5	Pos.	4+	4+	12.4	S+F

cells per 100 leukocytes. Sickle-cell preparation was positive, with 98% Holly shape and 2% filiform cells. Examination of the peripheral blood smear revealed normochromic erythrocytes, some of which were polychromatic; many macrocytes and normoblasts were seen.

Bone Marrow Examination.—A marked erythroid hyperplasia was present, with a myeloid-erythroid ratio of 1:5. Many sickle forms and target cells were seen. Blood type of the patient and of his mother was AcDe/c. Direct and indirect Coombs' tests were negative. VDRL test was negative. Liver profile revealed a total bilirubin of 19.4 mg. %, with 10.8 mg. % of the direct-reacting type; thymol turbidity, 5 units; cephalin flocculation, 3+ at end of 48 hours; total protein, 5.7 gm. %, with 4.3 gm. % of albumin and 1.4 gm. % of globulin. Roentgenograms of the chest showed no abnormalities. Skeletal x-rays revealed no unusual changes.

Course and Treatment.—Frequent blood cultures were obtained. These consistently revealed hemolytic Staphylococcus pyogenes var. aureus, coagulase-positive and resistant to all antibiotics except erythromycin, novobiocin, and chloramphenicol. The bacteremia was treated with tetracycline, penicillin, erythromycin, and novobiocin. The cultures remained positive despite large doses of these drugs. The patient's hematocrit value gradually decreased to 18%, with a hemoglobin of 6.4 gm. % and 1,870,000 red blood cells. He became dyspneic and took feedings poorly. He was then transfused with 60 cc. of whole blood. After this his condition improved somewhat, but his jaundice deepened and his total bilirubin rose to 69.6 mg. %, with 38.0 mg. % of the direct-reacting type. His thymol turbidity rose to 8 units, with an alkaline phosphatase of 2.0 units. His stools were described as yellow throughout this period. During the fifth week of his hospitalization, the patient became febrile. Two days after this fever his hemoglobin was found to be 5.4 gm. %, with 1,400,000 red blood cells. He was given a 50 cc. packed cell transfusion. During the procedure he became dyspneic. He improved in an oxygen hood. On the following morning, however, his respirations were grunting and crackling rales were heard in the right lung field. His condition gradually grew worse, and he died on the 44th day of hospitalization.

Postmortem Examination.—At post-mortem examination the major findings were limited to the lungs, spleen, liver, and kidney.

The lungs were atelectatic, and interstitial pneumonitis with thickening of the alveolar walls and infiltration of leukocytes and mononuclear cells was noted. The extrahepatic bile ducts were patent.

The liver microscopically showed the most pronounced findings. The lobular architecture was distorted. There was a proliferation of connective tissue. The interlobular reticulum was also thickened. The canaliculi were plugged with bile. The sinusoids were tremendously distended with bile pigment, causing marked destruction of parenchymal cells. There was some regeneration of liver cells, with the presence of multinucleated giant cells and scattered foci of hematopoiesis.

There was tremendous engorgement of the splenic sinusoids, with some hemorrhage. Marked sickling of the erythrocytes and areas of hematopoiesis and hemosiderin deposits could be seen throughout the spleen: however, no evidence of infarction or fibrosis was present.

The epithelium lining the proximal and distal tubules of the kidney was studded with golden-brown pigment granules. The distal and collecting segments contained disintegrating red cells.

Sickling was present in all organs examined but was most marked in the spleen and thymus.

CASE 2.—A 6-week-old Negro girl was admitted to the hospital on June 17, 1957. The primary difficulty was diarrhea of four days' duration. The only pertinent family history was that an 8-year-old sibling was said to have anemia. The patient was a well-developed, well-nourished girl, who appeared slightly pale. No jaundice was apparent. The liver and spleen were just palpable at the respective costal margins. The examination of the heart and lungs was negative.

Laboratory Examination.—Urinalysis, negative. Stool culture, 4+ Escherichia coli and 1+ Aerobacter species, negative for enteric pathogens. Blood: RBC, 2,700,000 per cubic millimeter; hemoglobin, 7.6 gm. %; reticulocytes, 2.8%; WBC, 8000 per cubic millimeter. Sickle preparation was positive 18.4% at the end of 15 minutes, 58% at 24 hours, and 77.8% at the end of 48 hours. The preparation could not be followed further because of drying. Differential smear of periph-

TABLE 2.—*Serial Hematologic Studies on Patient 2*

Date	Hb., Gm. %	Het., Cu. Mm.	RBC ×10⁶	Reticulocytes, %	MCH		Mean Cell Vol., Cu. μ	Alkali-Denaturation Value, %	Sickling (at 24 Hr.), %	Target Cells, %	Bone Marrow M:E Ratio
					Conc. %	μμg.					
5/10/57	17.0	49	5.1	..	34	33	96	..	..	..	3:1
6/18/57	7.6	23	2.7	2.8	33	28	85	63.5	77.8	10	1.4:1
6/30/57	7.1	19.0	2.18	..	..	..	..	..	..	..	..
7/1/57	7.4	19.0	2.1	..	38	35	90	64	90-95	..	..
7/9/57	8.0	23	2.5	3.2	..	..	..	..	..	..	..
8/9/57	7.5	22	2.6	8.0	34	28	84	42.5	..	20	0.8:1
10/1/57	6.6	22	..	..	..	..	..	21.3	98	23	..

eral blood: The erythrocytes were normochromic, normocytic. There were 10% target cells and an occasional poikilocyte resembling a sickle form. A rare nucleated red cell was seen. The leukocytes and platelets appeared normal. Serial hematologic observations are shown in Table 2. Direct and indirect Coombs' tests were negative. Liver profile: thymol turbidity, 0.5 units; direct-reacting bilirubin, 0.3 mg. %; total bilirubin, 0.6 mg. %. It was found that this patient had been studied previously in our laboratory for another purpose at 4 days of age. At that time the red blood cell count was 5,100,000 per cubic millimeter; hemoglobin, 17.0 gm. %, and hematocrit value, 49%. Her serum iron was 200μg. with an iron-binding capacity of zero; the per cent saturation was 100.

Course and Treatment.—The patient was given sulfisoxazole (Gantrisin) and was offered a formula of skimmed milk and a multivitamin preparation. Her diarrhea responded rapidly to this regimen, and a regular evaporated milk formula was again provided. Her hemoglobin and hematocrit values remained fairly stable during a month's observation in the hospital.

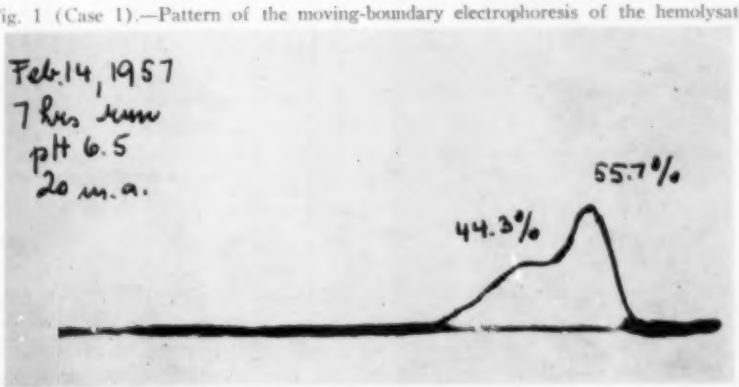
She was seen at 3 months of age and was doing well at that time. She was pale but not icteric. Her liver was palpable 2.0 cm. and the spleen, 1.5 cm. below the respective costal margins.

Results

Hemoglobin Analysis.—Figures 1 to 3 represent the hemoglobin analysis of these two patients. The hemolysate of Patient 1 was composed of 55.7% of hemoglobin S and 44.3% nonsickling hemoglobin by the Tiselius method. The hemolysate of the second patient was composed of 42.5% of hemoglobin S and 57.5% of nonsickling hemoglobin by the same technique. Close agreement was found between the percentage of fetal hemoglobin by moving-boundary electrophoresis and the alkali-denaturation method. By the latter, a value of 42.6% was obtained for Patient 1 and 59.5% for Patient 2. Follow-up observations on this second patient one month later revealed the same percentage of alkali-resistant hemoglobin. At this time, the sickling preparation was 90% to 95% positive after 24 hours' incubation (Table 1).

Family Studies.—Hematologic studies were performed on the other family members. The values for the family of the first patient are shown in Table 1.

Fig. 1 (Case 1).—Pattern of the moving-boundary electrophoresis of the hemolysate.



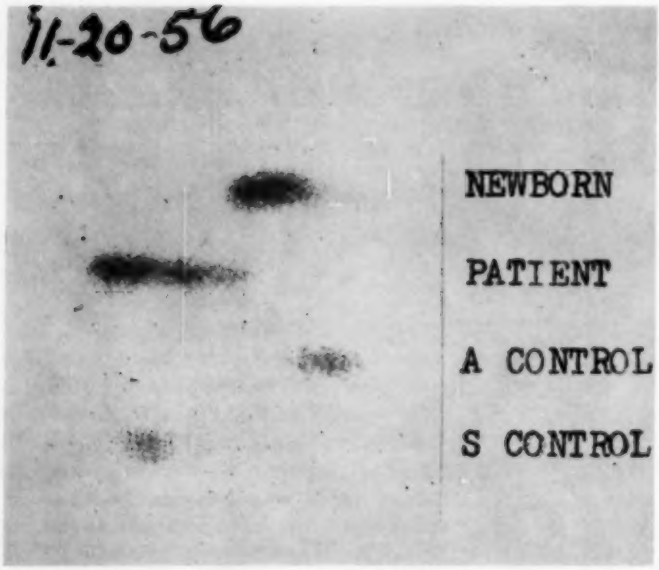


Fig. 2 (Case 1).—Pattern of the paper electrophoresis of the hemolysate.

The mother in this case also had a child by another man, who was found to have normal hematologic values and only hemoglobin A as determined by paper electrophoresis. Their son had only the sickling trait. Similar examinations of the blood of the members of the second patient's family revealed that the mother and father had the sickle-cell trait and that one daughter, previously described in the history, had

Fig. 3 (Case 2).—Paper electrophoresis patterns of the entire family.
Fig. 4.—Chromium survival of patients' erythrocytes.

Figure 3

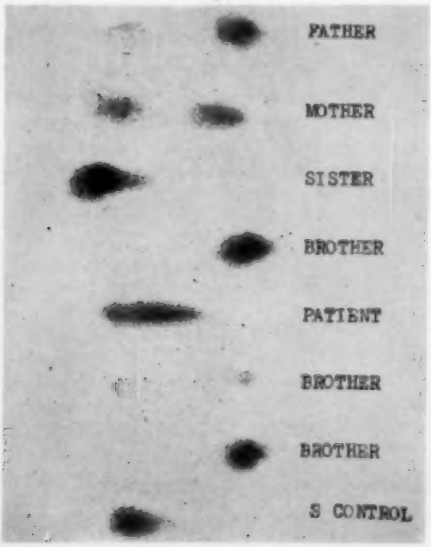
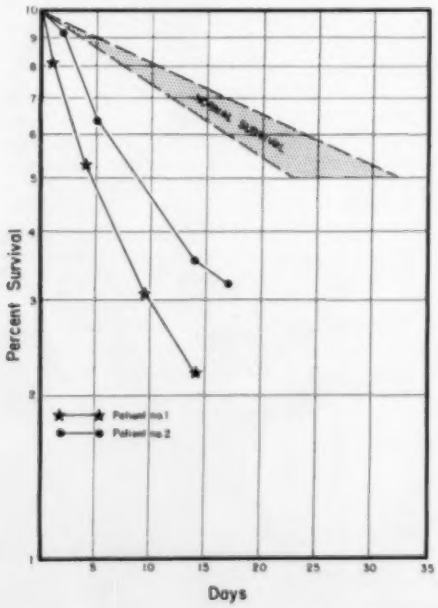


Figure 4



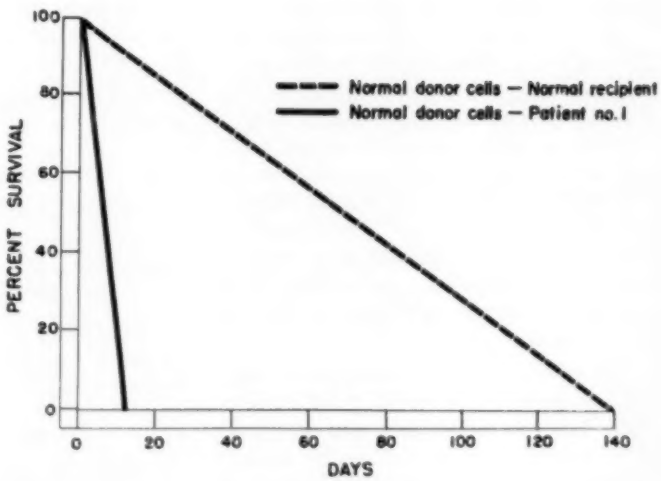


Fig. 5 (Case 1).—Ashby survival of normal cells in Patient 1.

sickle-cell anemia. The electrophoretic studies on this family are depicted in Figure 3.

Erythrocyte-Survival Studies.—Figure 4 shows the chromium survival of the red cells of these two infants compared with normal controls done in our laboratory. The half-lives of the red corpuscles were four and one-half and eight and one-half days, respectively.

Ashby survival study was also conducted on the first patient by taking fresh normal donor cells and injecting them into his circulation. These findings are depicted in Figure 5. The mean survival time of these cells was 10 days.

Comment

Only four previously described cases of sickle-cell disease have been reported in the first three months of life.[7-9]

One of these, the patient described by Cohen et al., was a one-month-old girl of Puerto Rican descent who had rather typical clinical and pathological stigmata of the disease, with the exception that there was no sickling in the other members of the family.

Wollstein and Kreidel[10] report a fifth infant who was said to have had "active sickle cell anemia" and who died of bronchopneumonia; however, they do not describe this patient in detail. Recently Watson[11] stated that cases of sickle-cell anemia in infants less than 4 months of age had not been observed by her.

The paucity of cases in this early age period compared with their abundance in older children, particularly after one year of age, is somewhat puzzling. Watson,[12] Switzer,[13] and Schneider[14] have found that the incidence of sicklemia in newborn Negro infants is the same as in the adult, i. e., in the range of 8%. Other authors[15,16] have found a lower percentage. All observers agree, however, that the percentage of sickling in vitro is less and the rate of appearance of these forms is slower than in the older child and adult. Watson's[12] explanation for this phenomenon was the fact that the infant's erythrocytes contained a large percentage of fetal hemoglobin, which does not allow complete expression of the sickling hemoglobin.

Harris[17] has shown that stroma-free solutions of sickle-cell hemoglobin when deoxygenated are very viscous. Spindle-shaped bodies, known as tactoids, can be seen by phase microscopy. It is probable that sickled erythrocytes are in essence "a hemoglobin tactoid, thinly veiled and somewhat distorted by the cell membrane." When a hemoglobin S solution of sufficiently high concentration

(above 10 gm. %) is exposed to a continuous stream of CO_2 gas to maintain the pigment in the reduced state, the hemolysate gels. Singer and Singer,[18] studying this gelling phenomenon, found that in vitro it required at least a minimum of 20 to 25 gm. % of hemoglobin S in an aqueous solution from a patient with sickle-cell anemia to produce a gel. Hemoglobins C and A decreased the amounts of hemoglobin S pigments necessary for gelling, and hemoglobin F exerted no significant influence on the gelling phenomenon.

The percentage of hemoglobin S in adults with sickle-cell trait varies from 22% to 45% and in sickle-cell anemia, from 76% to 100%, as determined by electrophoretic and alkali-denaturation methods.[19] The described patients' hemoglobin solutions were composed of 55.7% and 42.5% hemoglobin S. These are lower values than have previously been reported in patients with sickle-cell anemia.

From this, one can deduce that there is no critical percentage of hemoglobin S for the separation of sickle-cell anemia and sickle-cell trait. Furthermore, sickle-cell anemia does not appear to be dependent on a specific amount of this type of hemoglobin for the production of symptoms.

The mean corpuscular hemoglobin values in these two cases were 33.8% and 38.0%, respectively. Therefore, the concentrations were 18.8 and 16.1 gm. % expressed as hemoglobin S. This is in keeping with the observation that at least 10 gm. % of hemoglobin S is necessary to be present for the formation of tactoids.[17] However, it would suggest that in vivo lower concentrations than 20 gm. % of hemoglobin S in the cells of some patients with sickle-cell anemia may produce sickling. Further observations along this line would be worth while.

One disconcerting fact that must be considered is that the first patient had antibiotic-resistant bacteremia. The shortened survival of normal donor erythrocytes may have been due to this cause or to a splenic storage anemia.[20] This may have had some relation to the hemolysis and anemia. However, this would not, to our knowledge, have affected the sickling phenomenon. These complicating features did not appear to be present in our second case.

Summary

Two young infants with sickle-cell anemia are described. The percentages of hemoglobin S found in the babies were lower than those that have been described in older children or adults.

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Clinical Study of Four Hundred Twenty-Five Idaho Poliomyelitis Vaccine Recipients in 1955

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The explosive outbreak of poliomyelitis in Idaho among recipients of poliomyelitis (Salk) vaccine and their contacts in April, 1955, has been well documented by Peterson et al.[1] and by Langmuir and associates.[2] Epidemiological and laboratory evidence strongly indicates that the episode was triggered by faulty vaccine. The presence of viable poliomyelitis viruses in the vaccine which was used in Idaho has been reported.[1,3]

The purpose of this paper is to report on a further study of vaccine recipients. A unique situation existed in Idaho following the mass vaccine program in April, 1955. It was known that approximately 32,000 children were vaccinated between April 19 and April 27, when the vaccination program was discontinued. Only two lots of poliomyelitis vaccine from one manufacturer were utilized for the inoculations. By June 1, 1955, a total of 22 cases of poliomyelitis, which on epidemiological and laboratory evidence pointed to the vaccine as the direct cause, had been reported to the Idaho State Board of Health. It was apparent to health officials, practicing physicians, parents, and school officials that a wave of illness followed among the vaccinated children. The purpose of this study was to determine the extent of illness following vaccination; to determine, if possible, whether the vaccine caused the illness, and, if so, to determine whether nonapparent residual weakness or paralysis of muscle groups could be detected in the children.

Submitted for publication Nov. 11, 1957.

Practicing orthopedic surgeon (Dr. Shaw); Senior Assistant Surgeon with the United States Public Health Service at the time of study (Dr. Sunada); Director of Nurses with the Idaho State Board of Health (Miss Hopkey).

Method of Study

The cities of Pocatello, Boise, and Lewiston were chosen for study areas because local health units are located in these cities and therefore personnel and facilities were available for assistance in the study. These cities are widely separated geographically and located in the southeastern, southwestern, and north central portions of the state, respectively.

A total of 425 children are included in this study. The children ranged from 7 through 12 years of age and were all of white parentage. The sexes were equally represented, with 213 females and 212 males. Children were brought into the clinics voluntarily by their parents in the Pocatello and Boise areas. In the Lewiston area every third name was called on from a master list of the children who received the vaccine. All children received poliomyelitis vaccine in April, 1955. None of the children studied had been reported to the Idaho State Health Department as having contracted poliomyelitis during the previous year. In addition, children who had illnesses following vaccination who were called to our attention but had been investigated previously were not included in the study.

Blood samples were obtained from these children approximately six weeks after vaccination in order to determine their poliomyelitis neutralization antibody levels. The main portion of this study was initiated in November, 1955, and carried through February, 1956. A team consisting of a physician epidemiologist (K. S.), orthopedic surgeon (M. B. S.), nurse epidemiologist (I. A. H.), and three physical therapists visited the three areas chosen for study. The method of study consisted of thorough interviewing of the child and parent in regard to significant past medical history and the illness history following vaccination in April. Family history also was obtained with particular reference to any illness among unvaccinated members of the family following the vaccination program. The child then was seen by one of the three physical therapists for a complete muscle examination according to the method utilized in the 1954 poliomyelitis field trials as outlined by Jacobs.[4] The muscle examination was performed by the physical therapist without knowledge of

the history secured at the interview. Each child was seen by the orthopedic surgeon for a complete neurological and muscle grading examination. Finally, blood samples were obtained again from each child for poliomyelitis antibody levels to be compared with the blood samples drawn earlier.

School attendance records were examined in selected schools in the three areas. Schools selected were those with several grades in the same building. Daily attendance records of children were compared in those grades of children not vaccinated with those that were. Records were examined from two weeks prior to the vaccination program through one month after it.

Results

Presentation of the results of this study can best be shown by data secured through interview and the findings of the clinical examination. Antibody levels of these children and others are to be published in detail by Eklund [5] and will be mentioned only briefly here.

History of Illness.—Among the 425 children, a history of illness within a period of 3 to 25 days after vaccination was obtained from 160. Analysis of these 160 histories revealed 17 illnesses diagnosed by the attending physician at the time of illness as due to entities clearly not related to our study, e. g., mumps, measles, streptococcal sore throats, and others. In an additional four illnesses the histories were considered as too vague or inconsistent to be of value. After elimination of these 21 from the 160, a total of 139 children (32.7% of the children under study) were grouped as having had an illness with symptoms compatible with poliomyelitis. The remaining 286 (67.2%) children from the total of 425 were considered as a group not exhibiting any symptoms. Of the 139 children with a history of illness there were 77 boys and 62 girls. Fifty-nine (42.4%) of these children were seen by a private physician at the time of illness. Diagnosis in these instances ranged from "reaction to injection" to "summer virus."

A breakdown of the frequency of appearance of various symptoms in the group of 139 children is presented in Table 1.

TABLE 1.—*Frequency of Symptoms (139 Children)*

Symptoms	Children, No.	Per Cent of Total
Fever	120	86.3
Headache	95	68.3
Muscle pain	62	44.6
Sore throat	56	40.2
Stiff neck	43	30.9
Vomiting	36	25.8
Stiff back	25	17.9
Limp	16	11.5

Fever was the commonest symptom, occurring in 86% of the children, while 11% of the children were noted to limp after the illness. All of the children in the group gave a history of three or more of the symptoms listed.

The time of onset of generalized illness as represented by symptoms listed in Table 1 is graphically represented in Figure 1. One hundred three of the children had their onset of symptoms between the third and ninth days following vaccination. The median period between inoculation and onset of illness was approximately eight days.

Twenty-seven (19.4%) of the one hundred thirty-nine children gave a history of local reactions, e. g., swollen, reddened, or painful sites of inoculation. These reactions occurred one to three days following inoculation. In the group of 286 without general symptoms, a total of 25 (8.7%) gave a similar history. There were no histories of allergic reactions in either group.

Family Illness.—Only one family from the group of 286 children without symptoms gave a history of generalized illness among members other than the vaccinated child. On the other hand, from the group of 139 children with symptoms, 18 (12.9%) families gave a history of illness among other members. Ten of these families had more than one other member ill. Illness among family members always followed the illness of the vaccinated child. The onset of illness in families was from 8 to 30 days following inoculation of the vaccinated member of the family. The median time for onset of illness in family members was 15 days. Figure 2 graphically indicates the onset of illness in members of the family.

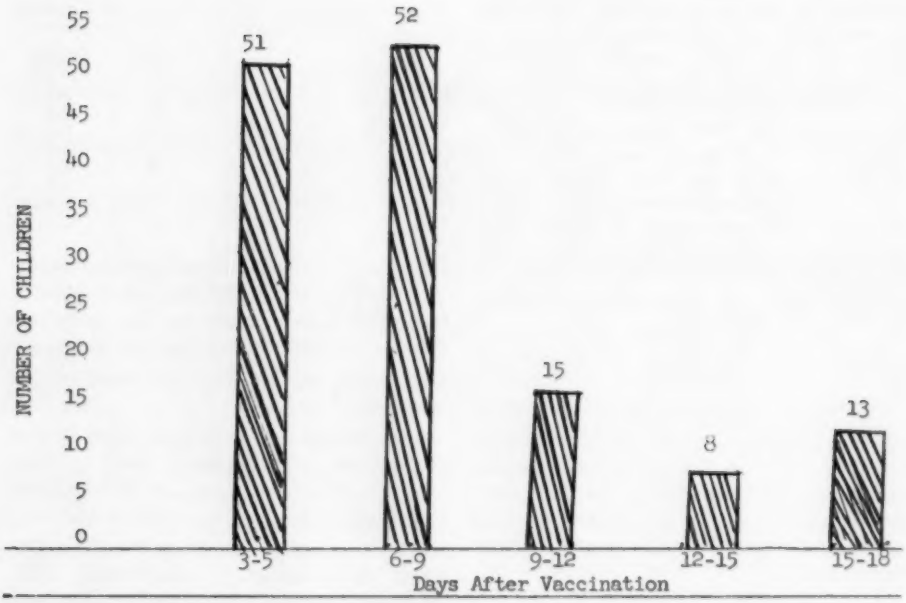

Fig. 1.—Onset of symptoms following vaccination in 139 children.

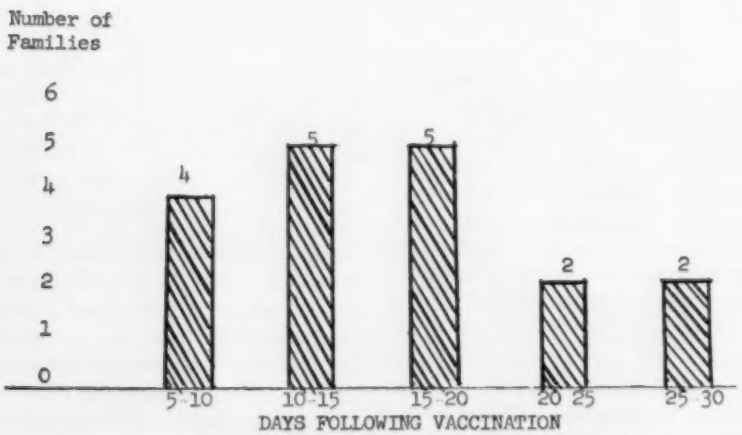

Fig. 2.—Onset of illness among family members of the vaccinated child.

Muscle Examination.—Examination of the children by physical therapists seven to nine months after vaccination indicates that those children with symptoms demonstrated a higher percentage of muscle weakness than those without. Table 2 summarizes these data and indicates that while 30.9% of the children with symptoms had some demonstrable weakness only 16.7% of the children without symptoms had any evidence of muscle weakness. The difference between these two groups is significant statistically by the χ^2-method.

Further comparison of the group with symptoms and the group without symptoms is presented in Table 3. Although there were

TABLE 2.—*Muscle Examination of 425 Study Children*

Group	Total	Normal Examination		Weakness Detected	
		No.	%	No.	%
Symptom group	139	96	69	43	30.9
No symptoms	286	238	83.2	48	16.7
x^2 11.1					

TABLE 3.—*Comparison of Muscle Weakness Found in the Symptom Group (139) and the Group Without Symptoms (286)*

Muscle Group	Children With Symptoms		Children Without Symptoms	
	No. with Weakness	%	No. with Weakness	%
Neck flexors	20	14.3	32	11.1
Shoulder girdle	10	7.1	7	2.4
Abdominal	15	10.7	18	6.2
Hip girdle	11	7.9	5	1.7

weaknesses found in other muscle groups than those listed, they were infrequent. It is apparent that there was a difference in occurrence of muscle weakness in the two groups, with the greatest discrepancy found in the hip girdle muscles (7.9% as compared with 1.7%).

Tightness of heel cords and back and hamstring muscles was recorded frequently in both groups of children. There were 66 children (47.7%) in the group with symptoms who demonstrated tightness of one or more of the areas mentioned above. From the group of children without symptoms a total of 110 (38.4%) were classified as showing tightness in one or more of these areas.

Antibody Studies.—Blood samples were obtained from these children approximately six weeks after vaccination and again at time of muscle examination—seven to nine months after vaccination. With realization that the children were exposed to the poliomyelitis virus during the 1955 summer during this interval, a comparison of the second blood sample was made with the first. In only one instance it was noted that a child had developed antibody to poliomyelitis (Type I) which was not present in the first sample. There were no significant rises in titer of any of the other paired specimens.

In the total group of 407 specimens, 284 (69.7%) were positive for Type I antibodies while 362 (88.9%) and 265 (65.1%) were positive for Type II and Type III, respectively. There did not appear to be any significant statistical difference in the frequency of any of the antibody types in the two groups of children. In the group with symptoms 130 specimens were examined. Of these, 95 (73%) were positive for Type I; 117 (90%), for Type II, and 95 (73%), for Type III. In the group without symptoms after vaccination there were 277 specimens examined. Of these 189 (68.2%) were positive for Type I; 245 (88.4%), for Type II, and 170 (61.3%), for Type III. A titer of 1:8 or greater was considered necessary to be considered positive in all specimens.

Comment

Retrospective studies of this nature present weaknesses which are known to all investigators. The circumstances in this episode, however, prohibited any other method. This was an instance in which we knew that the poliomyelitis vaccine contained live virus, we knew the exact date of exposure, and we knew that clinical paralytic cases of poliomyelitis had occurred. Only those with severe illness were reported to the State Health Department as cases of poliomyelitis. We, therefore, in this study hoped to determine the extent of illness among the vaccinated children which was not reported as poliomyelitis. Clinically, the illness was compatible with nonparalytic poliomyelitis. The clarity with which parents recalled incidents following the vaccination program was not surprising. Owing to the extensive publicity over radio and press given to the episode, the events were firmly entrenched in the parents' minds. It is our opinion that the histories were extremely reliable.

Approximately 32% of the children in this study gave a history of illness following vaccination. The occurrence and frequency of illness were essentially the same in all areas. The onset of illness among the children epidemiologically was characteristic of an outbreak arising from a common source, with the majority of cases occurring in the first few days of the epidemic curve and a gradual decrease in the number of cases. Additional support was gained for the concept that this illness was peculiar to the vaccinated children by examination of school attendance records in the three areas. In those children not vaccinated we found no unusual decrease in attendance after the vaccination program, whereas the opposite was true for the vaccinated children. In many instances there is intermingling of children of several grades. It is our opinion that if this illness had been unrelated to the vaccine it also would have been reflected correspondingly in the attendance records of children in grades above and below those of the vaccinated children.

The reasons for reactions at the site of injection are not clear. We disregarded any complaints of reactions at the site within the first 24 hours after injection. The complaints tabulated occurred 24 to 72 hours after the injection and consisted of pain, swelling, or reddness at the site of injection. The majority recalled all three findings. Investigation of actual paralytic cases which occurred following vaccination by one of us (K. S.)[6] did not indicate that a local reaction was a common finding. There was a definitely higher percentage (19.4%) of children with local reactions among those who later reported generalized symptoms than among those who did not (8.7%). There was no indication that those reporting local reactions demonstrated weakness in the inoculated extremity oftener than those who did not complain of local reactions.

Illness among family members other than the vaccinated member followed in 18 of the 139 families in which the vaccinated child became ill. In all instances the illness of an unvaccinated family member followed the illness of the vaccinated child. It is interesting that the onset of illness in the unvaccinated member occurred approximately 15 days after vaccination, or approximately 8 days after the illness in the vaccinated child. This onset leads us to the conclusion that it represents a "double incubation" period.

Approximately 30% of the children with symptoms showed evidence of muscle weakness. On the other hand, since weakness was demonstrated in 16% of those without symptoms, it is difficult to state how much of the weakness in the children with symptoms was attributable to the illness, even though it is evident that those with symptoms did show a significant statistically higher percentage of weak muscles. Since 98% of the children in the eligible age group received the vaccine during the mass immunization program, it was not possible to secure a comparable "control" group of children in Idaho who did not receive the vaccine.

Epidemiologically, the evidence presented indicates to us that the illness of the children following vaccination was related to the use of poliomyelitis vaccine containing live virus. Clinically, the illness is compatible with a diagnosis of abortive poliomyelitis. A definite diagnosis of poliomyelitis can be made only by laboratory means. Circumstances were not such that blood specimens were secured prior to vaccination. There is no way to tell, therefore, what percentage of these children already had antibodies against one or more of the poliomyelitis types. If this had been possible, there might have been a correlation of symptoms with antibody levels. The lack of correlation in this instance does not rule out the diagnosis, however.

Summary

A clinical study of 425 children who received poliomyelitis vaccine containing live poliomyelitis virus in April, 1955, in Idaho is presented. A total of 139 (32.7%) of these children gave a history of illness compatible with abortive poliomyelitis within 3

to 25 days after vaccination. A statistically higher percentage of children who reported symptoms had demonstrable muscle weaknesses (30.9%) as compared with those who had no symptoms (16.7%).

The Idaho State Health Department and Mr. L. J. Peterson, former director of the Department, cooperated in this study. Without the aid and suggestions of the many members of the State Health Department and Local Health Units this study would not have been undertaken. Members of the Communicable Disease Center's Poliomyelitis Surveillance Unit, U. S. P. H. S., gave suggestions. The physical therapists who aided us in this work are Miss Anne Sweely, Mr. Glenn Darnell, Mrs. Phillis Lomax, and Mrs. Perry Swisher. Dr. Carl Eklund, Medical Director, Rocky Mountain Laboratories, U. S. P. H. S., Hamilton, Mont., and Mr. Ralph Carpenter, Assistant Director, Division of Preventive Medicine, Idaho State Board of Health made criticisms and suggestions.

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The Natural History of Mental Deficiency in a State Hospital

I. Probabilities of Release and Death by Age, Intelligence Quotient, and Diagnosis

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The diagnosis of mental deficiency places serious responsibilities upon the pediatrician. He must assist the parents in planning for the long-term care of their defective child. Although the parents must ultimately decide whether to keep their child at home or to seek his admission to an institution, the pediatrician is frequently the most important counselor in helping them to reach a decision. The more information he has available the easier will be his task in discussing institutional admission. Unfortunately, however, adequate data are very limited on the natural history of the institutionalized mentally deficient patient.[1]

It is the purpose of this paper to provide information concerning the probabilities of release and death of patients admitted to a state hospital. The data were collected as part of a study of patients admitted to Pacific State Hospital during the period of July 1, 1948, to June 30, 1952. The results and the methodology have been reported elsewhere in greater detail.[2-4]

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Presented in part before the Western Society of Pediatric Research, San Francisco, October, 1957.

Superintendent and Medical Director, Pacific State Hospital, and Associate Clinical Professor, Department of Psychiatry, University of California School of Medicine at Los Angeles (Dr. Tarjan); Assistant Professor, Department of Pediatrics, University of California School of Medicine at Los Angeles, and Research Consultant, Pacific State Hospital (Dr. Wright); Chief, Biometrics Branch, National Institute of Mental Health, Public Health Service (Dr. Kramer); Analytical Statistician, Biometrics Branch, National Institute of Mental Health, Public Health Service (Mr. Person); Statistical Research Officer, Department of Mental Hygiene, State of California (Mr. Morgan).

Methods

Pacific State Hospital is a California facility for the care and treatment of the mentally deficient. During the period involved there was an average daily resident population of about 1900, with 1169 first admissions. Patients who were admitted for immediate transfer to another state hospital or for observation or who were found not mentally deficient were excluded from this study. The remaining 722 first admissions, of whom 416 were males and 306 were females, were then processed to determine the probabilities of death and live release. Each patient was followed for four years, and the last observations were made on June 30, 1956.

"Live release" was defined as the first departure of the patient from the hospital with the intent that the patient not be returned. This includes release either to his own family or a foster home or to a vocational situation developed by the social workers. Also included among the live releases were patients who escaped and remained away from the hospital for at least 30 days. Experience has shown that these "escaped" patients usually made a reasonable and lasting adjustment. Returns from live releases were not reentered into the study group. Temporary departures from

the hospital known as "definite" leaves were not counted as live releases. During the eight-year period of the study there was an approximate annual average of 1500 definite leaves, increasing from 1127 during the fiscal year of 1948-1949 to 2450 during 1955-1956.

The clinical diagnosis, the patient's age on admission, his I. Q., and sex were studied in relation to their effect on population movement. Since sex was not strikingly related to the probability of death or live release in the entire population under study, no further report is given on this variable in this paper. Clinical diagnoses were made according to the nomenclature of the American Association on Mental Deficiency.[5] The intelligence quotients (I. Q.) used in the study were obtained from psychological examinations at the time of admission. The tests were those considered most appropriate for each patient by the examining psychologist.

TABLE 1.—*Median Age and I. Q. by Diagnosis, First Admissions to Pacific State Hospital, Pomona, Calif., 1948-1952*

Diagnosis	Patients		Median	
	No.	%	Age, Yr.	I. Q.
All patients	722	100.0	13.03	42.86
Developmental cranial anomaly	49	6.8	4.90	17.50
Mongolism	62	8.6	5.29	31.33
Due to infection	71	9.8	10.13	31.67
Due to trauma	120	16.6	11.50	28.16
Due to epilepsy	25	3.5	14.75	50.91
Familial	114	15.8	14.91	57.08
Undifferentiated	199	27.6	15.30	52.80
All other diagnoses	60	8.3	8.50	17.27
Diagnosis undetermined	22	3.0		

Results

Tables 1, 2, and 3 describe the diagnostic, age, and I. Q. characteristics of the 722 patients at the time of first admission. As noted in Table 1, over 40% of the patients were in two diagnostic categories: "familial" and "undifferentiated mental deficiency." Patients were diagnosed as "familial" when there was another person with mental deficiency present in the immediate family and if there was no clearly defined cause to account for either the patient's condition or the condition of the other family member. The diagnosis of undifferentiated mental deficiency was made when no other classification was appropriate. The "due to epilepsy" group included patients in whom mental deficiency may have been caused by or was coexistent with epilepsy and where no other specific cause accounted for both conditions. The remainder of the diagnostic categories are self-explanatory.

TABLE 2.—*Median I. Q. by Age, First Admissions to Pacific State Hospital, Pomona,, Calif., 1948-1952* *

Age, Yr.	Patients, No.	Median I. Q.
All patients	722	42.86
0–4	128	19.03
5–9	137	21.94
10–13	126	49.47
14–15	111	57.24
16–17	94	57.55
18–24	75	54.28
25–34	36	39.17
35 and over	14	40.00
Unknown age	1	

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The total group had a median age of 13.03 years and a median I. Q. of 42.86 (Table 1). The familial and undifferentiated groups had a higher median age and I. Q. than did the total group. Patients with developmental cranial anomalies and Mongolism had the lowest median ages on admission, about 5 years of age in each group.

It will be noted in Table 2 that patients admitted in the age range 14 to 18 years had a higher median level of intelligence (I. Q. 57) than those admitted at younger ages. The youngest age group was found to have the severest degree of deficiency,

TABLE 3.—*Median Age by I. Q., First Admissions to Pacific State Hospital, Pomona, Calif., 1948-1952* *

I. Q.	Patients, No.	Median Age, Yr.
All patients	722	13.03
0–19	168	6.83
20–29	75	7.64
30–39	78	11.67
40–49	91	14.65
50–69	225	15.28
70 and over	57	16.28
Unknown I. Q.	28	7.00

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AGE

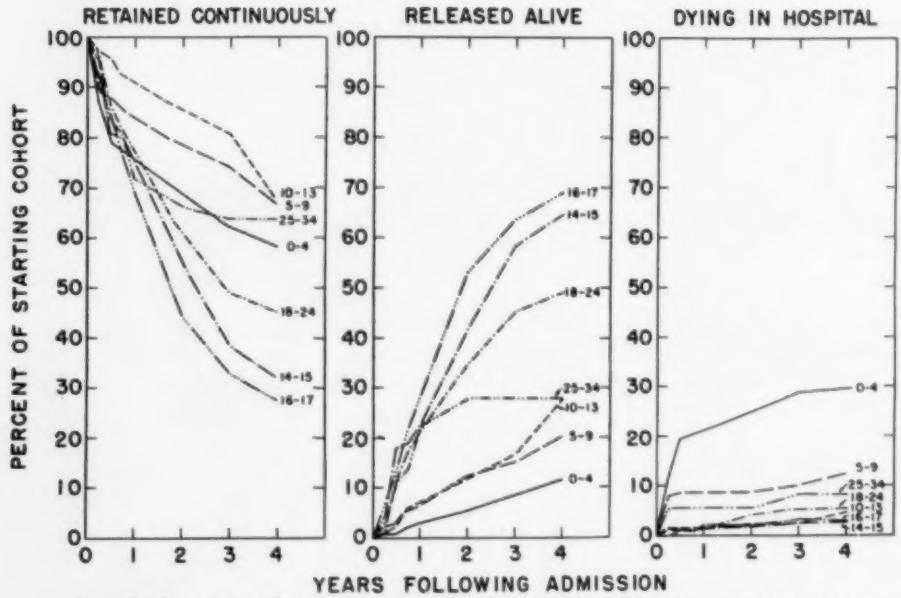

Chart 1.—Per cent of first admissions retained in hospital, released alive, and dead within specified periods following admission to Pacific State Hospital, Pomona, Calif., 1948 to 1952. (Reprinted with permission from the *American Journal of Mental Deficiency*.)

INTELLIGENCE QUOTIENT

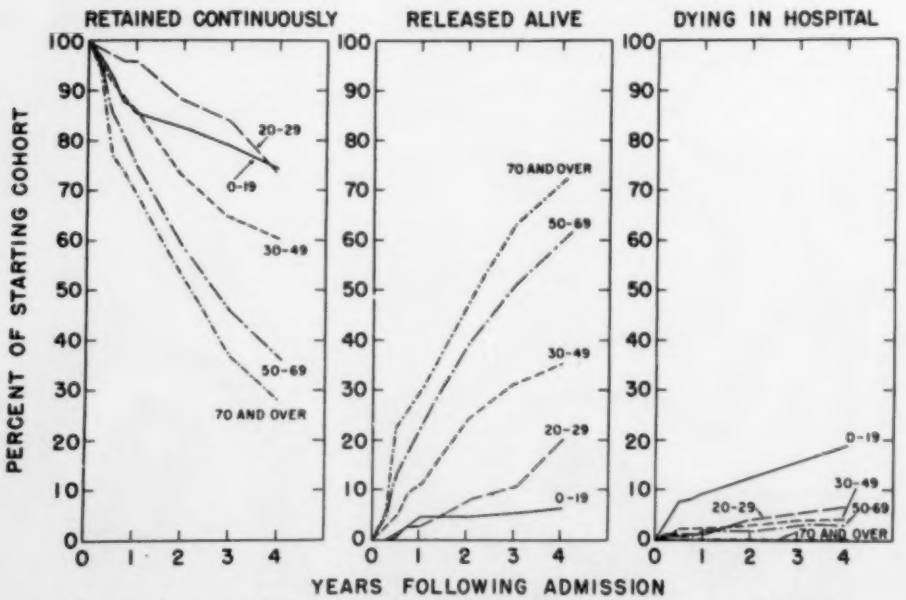

Chart 2.—Per cent of first admissions retained in hospital, released alive, and dead within specified periods following admission to Pacific State Hospital, Pomona, Calif., 1948 to 1952. (Reprinted with permission from the *American Journal of Mental Deficiency*.)

with a median I. Q. of 19. This relationship between age and I. Q. is also apparent from Table 3, which shows that the patients with the higher I. Q.'s (50 and over) were generally the older patients.

Charts 1, 2, and 3 give the cumulative percentages of deaths, live releases, and the likelihood of continuous retention in the hospital during a four-year follow-up period according to three variables: age, I. Q., and diagnosis.

In order to simplify presentation of these charts, only certain groups will be identified in the text. In Chart 1, the age groups 0 to 4 years and 14 to 17 years, a total of 333 patients, show obvious differences. The younger group showed a low cumulative release rate, with only 12% released in four years, and a high cumulative death rate, with 20% having died during the first year of hospitalization and 30% by the end of the fourth year. In contrast, the adolescent patients, 14 to 17 years of age, were released relatively rapidly, with nearly 70% being released at the end of four years. The death rate in this group was the lowest in the total population, about 3%, at the end of the four-year period.

Two groups in Chart 2 may be compared, namely, the 168 patients with I. Q.'s 0 to 19 and the 282 with I. Q.'s of 50 and over. The patients with quotients of 0 to 19 show characteristics similar to the younger age groups, with a low live-release rate, 6%, and a high mortality rate, 19%, by the end of four years. In contrast, the mildly deficient group, with an I. Q. of 50 or over, shows a four-year cumulative release rate of 62% and a cumulative mortality rate of 3%.

In Chart 3 live-release and mortality rates of patients with developmental cranial anomalies or Mongolism are very similar and contrast sharply with the rates for patients with familial or undifferentiated men-

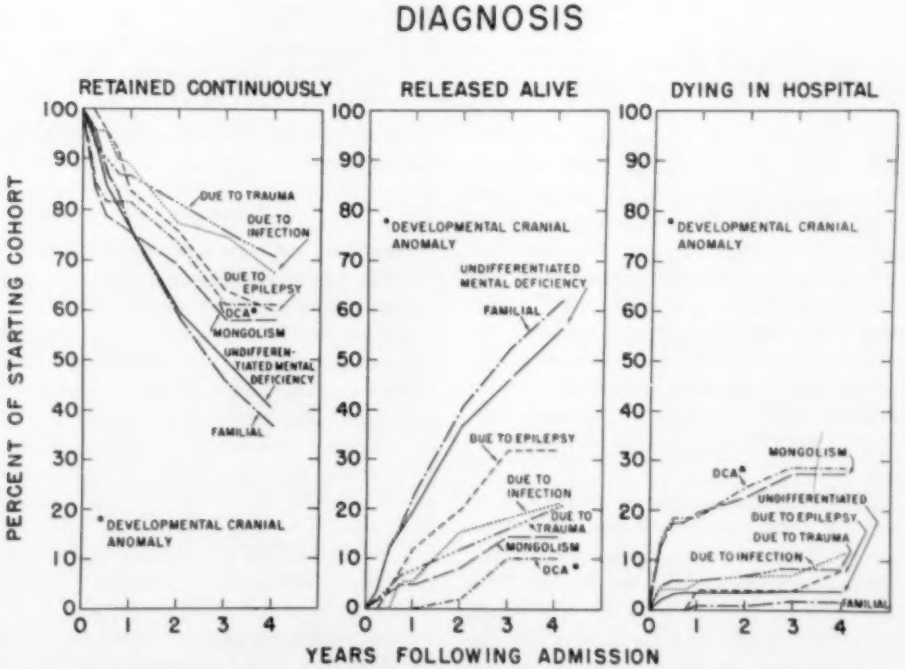

Chart 3.—Per cent of first admissions retained in hospital, released alive, and dead within specified periods following admission to Pacific State Hospital, Pomona, Calif., 1948 to 1952. (Reprinted with permission from the *American Journal of Mental Deficiency.*)

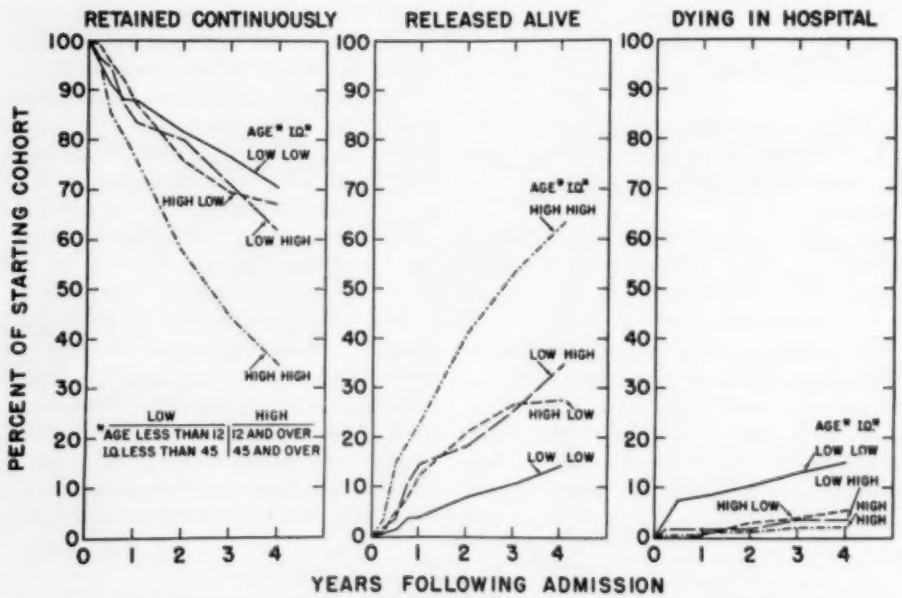

Chart 4.—Per cent of first admissions retained in hospital, released alive, and dead within specified periods following admission to Pacific State Hospital, Pomona, Calif., 1948 to 1952. (Reprinted with permission from the *American Journal of Mental Deficiency.*)

tal deficiency. The four-year cumulative live-release rate for patients with Mongolism was 15%, and this rate for patients with developmental cranial anomalies, 10%. The cumulative four-year death rates for these two groups were nearly identical (about 28%), with the majority of deaths occurring in the first year of hospitalization. In contrast, the familial and undifferentiated groups had cumulative live-release rates of 61% and 56%, respectively, and death rates of 4% and 2%, respectively, for the four-year period.

Chart 4 relates the probabilities of death and live release with a combination of two variables: age and I. Q. The population was divided into four groups by the age limit of 12 and the I. Q. value of 45. The results again demonstrate that the chances for survival are most impaired in the young and severely deficient patients, whereas the chances of release are best in patients over 12 years of age with a smaller degree of deficiency.

Comment

There are an estimated 2,000,000 to 3,000,000 mentally deficient persons in the United States, of whom about 150,000 are in public institutions.[6] Several physicians may be consulted by a family prior to the admission of a child to an institution. Parents frequently complain to hospital staffs that pediatricians make arbitrary recommendations, insisting either on admission or on keeping the child at home. Many physicians, however, do not have adequate information on the program of the nearby institution, nor do they have data available similar to those presented in this paper.

Parents are frequently not apprised of the difficult adjustment period which their child will undergo upon admission to a large institution. They are not made aware of

the chances of death during the first year of hospitalization, particularly in young severely retarded patients with Mongolism or developmental cranial anomalies, e. g., hydrocephaly and microcephaly. The statistics presented in this paper emphasize the need for counseling along these lines.

Institutionalization sometimes is considered a permanent solution, both for the child and for the emotional turmoil of the family. The data presented reveal that a substantial number of patients leave the hospital within four years, particularly in the adolescent group with mild degrees of deficiency. It does not seem advisable, therefore, in counseling parents, to emphasize the permanency of institutionalization for this group of patients.

Although the figures presented here are applicable only to Pacific State Hospital, and only for patients admitted between 1948 and 1952, it is likely that such factors as chronological age, I. Q., and diagnosis have a similar effect upon probabilities of death and release of mentally deficient patients in any institution. In addition to the variables studied here, mortality and release rates will depend upon many other factors, e. g., such characteristics of the patient as physical abilities, degree of personal hygiene, nutritional state, and personality structure; the constellation of the patient's family; the program of the hospital, and the availability of community resources. It is likely that release and death rates change from time to time in the history of any hospital, and they may vary from institution to institution.

The data presented also have important implications in the development of state hospital programs. Improved admission facilities and selected programs for the care and treatment of the newly admitted patient would probably decrease mortality rates. Intensified treatment programs and the development of additional community facilities may significantly improve release rates.

These investigations are being continued,* and such factors as neuromuscular development, ambulation, selected personality traits, characteristics of the family constellation, and community attitudes and resources will be examined as to their relationship to the likelihood of admission to a state hospital, the probabilities of death and release, and the prospect for adequate community adjustment upon discharge. The results will be reported intermittently, with the hope that the data will enlarge our understanding of the natural history of mental deficiency.

Summary

Data are presented on selected characteristics of patients admitted to a hospital for the mentally deficient. The patients were followed for a four-year period, and relationships of clinical diagnosis, age, and intelligence quotient to death and live release were analyzed. The implications of these data in the counseling of parents and in the development of treatment programs are discussed. Reports on the other facets of the natural history of mentally deficient patients are planned for the future.

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Case Reports

Recurrent Pannicular Hemorrhages

A Fatal Disease Related to Thrombotic Thrombocytopenic Purpura

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Introduction

We have recently observed an infant girl suffering from a prolonged, eventually fatal, illness which in some respects simulated thrombotic thrombocytopenic purpura. However, the clinical picture, the laboratory data, and even the histologic findings were so puzzling that they defied the diagnostic resources of all who saw her, including the staffs of two pediatric teaching centers. Since a review of the literature uncovered no comparable disorder, we feel justified in reporting and discussing a single case.

Report of Case

A white infant girl was born on June 30, 1954, three weeks past term. The mother had been in good health during pregnancy except for an attack of "pleurisy" during the seventh month for which she had been treated with sulfonamides. The family history contained nothing of interest. The parents were young and not consanguineous. Two subsequently born boys have remained healthy to date. Nothing unusual was noted at birth. When the patient was 3 weeks old the parents discovered that both eyes looked cloudy and consulted an ophthalmologist. They were informed that the child was nearly blind and that the condition was not amenable to treatment. Amblyopic nystagmus developed soon and persisted throughout life. The eyes were later described as follows (Dr. B. R. Sakler, Cincinnati) *: "Examination shows bilateral microcorneae. The right pupil is fixed. The pupillary opening is completely obstructed by a quadrilateral involvement of the posterior surface of the cornea. The anterior chamber is completely obliterated. The left eye shows a very shallow anterior chamber with the iris bulging forward. The pupil, dilated with difficulty, reveals a greyish-white mass which makes fundoscopic examination impossible. Summary: The findings present a bizarre developmental phenomenon. There is no definite syndrome into which we might fit this case."

At the age of 2 months the girl developed the first of many skin lesions, which were to be the most prominent feature of her illness. The lesion consisted of a dime-sized flat, reddened, indurated, and very tender area on the lower abdomen. Within three days the tenderness, redness, and swelling had disappeared, leaving a greenish-yellow discoloration. Two days later a new lesion appeared on the opposite side. It followed a similar course, appearing suddenly and fading out gradually after a few days. The subsiding lesions, when first seen by one of us, looked rather insignificant, somewhat like insect bites, bruises, or, possibly, small areas of fat necrosis. Oral and parenteral antibiotics (penicillin, streptomycin, and tetracycline) neither affected the evolution of the lesions nor prevented the appearance of new ones. No drug sensitivity or tolerance was noted at any time.

Two weeks after the first lesion the infant suddenly developed a larger, extremely painful and tender, induration involving one of the labia majora. It now appeared that these lesions might be the result of some type of vascular occlusion. Because of the puzzling picture the infant was referred to the Cincinnati Children's Hospital (under the care of Dr. H. C. Shirkey).

First Hospitalization.– Sept. 26 to Oct. 14, 1954.

Repeated laboratory examinations revealed the following: hemoglobin, 9.1 to 9.4 gm.; erythrocytes, 3,070,000 to 3,100,000 per cubic millimeter; reticulocytes, 4.6% to 6.2%; platelets, 297,000 to 319,000 per cubic millimeter; leukocytes, 10,600 per cubic millimeter, with 4% neutrophils, 2% eosinophils, 1% basophils, 49% lymphocytes, and 5% monocytes. The bleeding time was initially 15 minutes; a few days later, 9½ minutes; coagulation time was 4 minutes; plasma prothrombin, 100% of normal.

Submitted for publication Feb. 9, 1958.

From the Yellow Springs Clinic (Dr. Robinow); the Children's Hospital, Columbus, Ohio, and the Department of Pathology, Ohio State University College of Medicine (Dr. Newton).

* All the physicians named in this report gave permission to use their records and to quote from their statements.

The Coombs test was negative. Total bilirubin was 0.2 mg. %. The antistreptolysin titer was 50 units. A serum test for syphilis was negative. An examination of spinous process bone marrow was summarized as follows: "The two most prominent features are 1) moderately intense normoblastic activity, and 2) the presence of a large number of lymphocytes. The megakaryocyte-platelet system appears normal." A biopsy of one of the skin lesions was reported by Dr. B. H. Landing as follows: "Multiple cuts of a small piece of skin show no abnormal features except for one vessel, probably an arteriole, with elevation of the intima by three acidophilic hyaline masses, over which the intima appears to be stretched. No inflammation of the wall of this vessel or the surrounding tissue is seen and there is no evidence of thrombosis. The appearance is that of 'thrombotic thrombocytopenic purpura' rather that that of anaphylactoid purpura."

During the hospital observation period the infant continued to produce new transient skin lesions on the lower abdomen and thighs. Treatment with corticosteroids was recommended and was accomplished soon after discharge. It was repeated on several subsequent occasions. Neither corticotropin (ACTH) nor cortisone in adequate dosage had a noticeable effect on the appearance, severity, or evolution of the lesions or any of the accompanying phenomena (except possibly during the third hospitalization, see below).

The parents, understandably disappointed, now changed physicians in rapid succession. One of these (Dr. R. C. Hiestand, Springfield, Ohio) admitted the child to another hospital.

Second Hospitalization.—Mercy Hospital, Springfield, Ohio, Oct. 20 to Dec. 10, 1954.

On admission the child was found to have a severe anemia. Hemoglobin was 6.9 gm.; erythrocytes, 2,550,000 per cubic millimeter. Two transfusions raised these levels to 11.9 gm. and 4,310,000, respectively, on Oct. 29, after which time the values fluctuated but slightly. Bleeding time on admission was seven minutes; clotting time, five minutes. Platelet counts ranged from 86,000 per cubic millimeter on Oct. 22 to 1,037,000 on Nov. 14. Leukocyte and differential counts were always normal. An attempt to demonstrate L. E. cells was unsuccessful. On Dec. 3 an old and a new skin lesion were biopsied. The principal features were summarized as follows (Dr. M. Hunter): "There is evidence of hemorrhage in both nodules with deposition of hemosiderin and hematoidin pigment in the old nodule. No evidence of thrombi could be found in the blood vessels and no other specific pathology could be seen."

During this period of hospitalization new skin lesions occurred from time to time. The areas

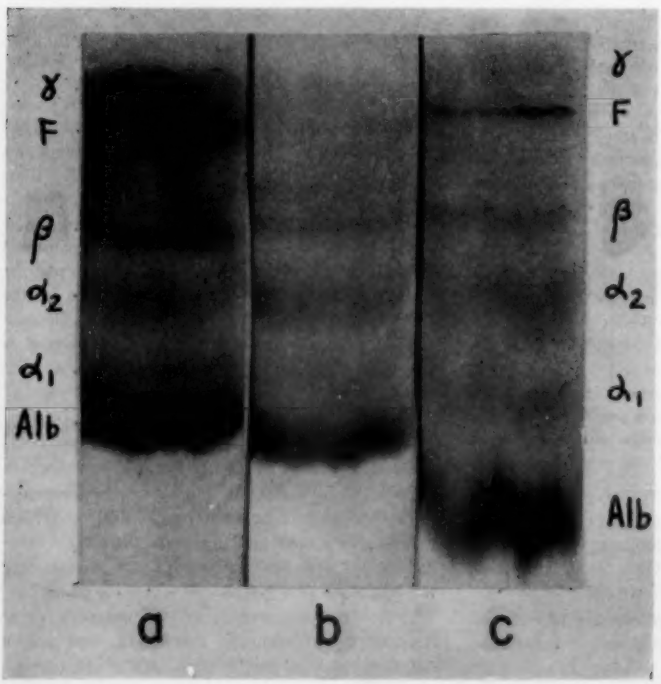


Fig. 1.—Paper electrophoresis of plasma (Dr. G. Zweig, formerly of the Kettering Institute, Yellow Springs, Ohio), showing α_1-, α_2-, β-, and γ-globulin fractions. *F*, fibrinogen; *Alb*, albumin. (*a*) Control strip; healthy adult. (*b*) Patient's plasma on Dec. 7, 1955. Note virtual absence of fibrinogen. (*c*) Patient's plasma on Feb. 9, 1956. Note slightly reduced fibrinogen.

involved gradually became somewhat larger, and most lesions now showed in addition to the redness some purpuric discoloration.

On Nov. 8 the patient was seen by a hematology consultant (Dr. B. K. Wiseman, Columbus, Ohio), who felt that the condition represented a form of anaphylactoid purpura, and on Dec. 10, 1954, the child was discharged with this diagnosis.

For nearly a year thereafter the girl developed normally, and her health remained satisfactory except for the continued occurrence of skin lesions.

About Nov. 1, 1955, the parents noticed a little bright red blood in the stools. This was observed repeatedly during the next five weeks. Though the parents later recalled that the girl had bled easily on some previous occasions, they did not become really alarmed until Dec. 6, 1955, when she fell and a seemingly minor cut of the tongue would not stop bleeding. When the girl was seen in the office the bleeding had continued for over 24 hours in spite of local cauterization and an injection of vitamin K given elsewhere. Laboratory studies showed hemoglobin to be 8.5 gm.; erythrocytes, 3,600,000; platelets, 119,000 per cubic millimeter. Venous blood failed to clot after several hours. Plasma electrophoresis showed complete absence of fibrinogen (Fig. 1). The child was now referred for emergency treatment and further study to the Columbus Children's Hospital.

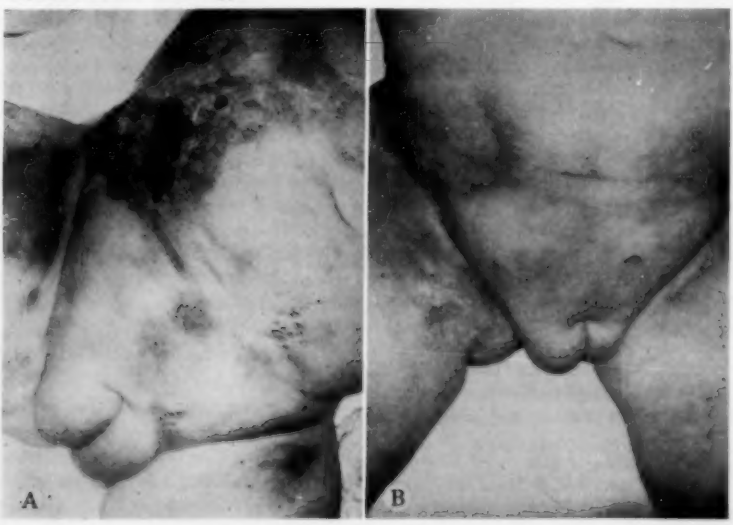
Third Hospitalization.—Dec. 7, 1955, to Jan. 7, 1956.

On admission in the evening the child was still bleeding from the tongue and there were ecchymotic areas with slight bloody seepage where heel and elbow had been punctured earlier for blood studies. There was a purpuric indurated area of skin involving a large part of the left lower abdomen, external genitalia, and left thigh (Fig. 2, *A*). During the night the temperature rose to 103 F; the pulse, to 180 to 200, and the child went into shock. An intravenous infusion was started, and after the administration of more than 200 ml. of whole blood pulse and blood pressure became stabilized and the patient rallied. After progressing reasonably well for the next two days she went again into shock on Dec. 10 and recovered once more after receiving 250 ml. of blood and 150 ml. of plasma.

On Dec. 8 the bleeding time was more than 10 minutes; the clotting time, 8 minutes. Throughout the hospitalization blood clots formed poorly and often dissolved on standing. The patient's serum digested gelatin film after incubation. These findings strongly suggested the presence of a fibrinolysin. A more detailed analysis of the clotting mechanism (by Dr. G. Y. Shinowara) a few days later, on Dec. 13, revealed normal fibrinogen, normal plasma thromboplastin component concentration, and prothrombin 90% of normal. The Coombs test was again negative.

On Dec. 9 tibial bone marrow showed "megakaryocyte hyperplasia with evidence of decreased platelet function" (W. A. N.). A tourniquet test was negative. Platelets rose from 80,000 per cubic millimeter on admission to 193,000 on Dec. 13, to drop again to a low of 43,000 on Jan. 6, but no

Fig. 2.—*A*, photograph of abdomen and thigh, Dec. 21, 1955, showing hemorrhages into the subcutaneous tissue with secondary necrosis. *B*, repeat view of abdomen and thigh, Jan. 17, 1956, after radiation therapy.



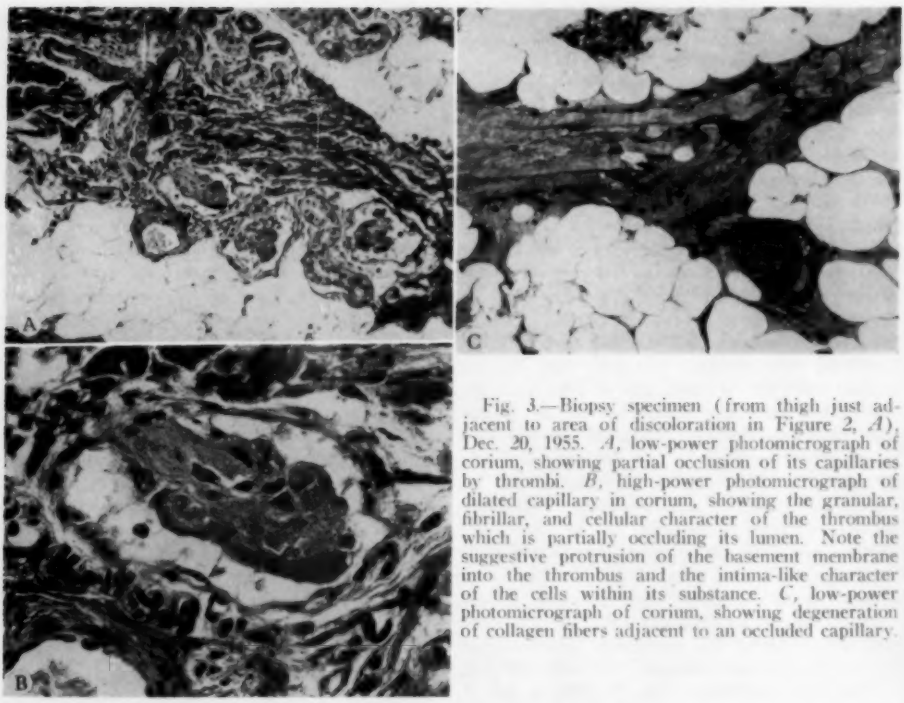


Fig. 3.—Biopsy specimen (from thigh just adjacent to area of discoloration in Figure 2, *A*), Dec. 20, 1955. *A*, low-power photomicrograph of corium, showing partial occlusion of its capillaries by thrombi. *B*, high-power photomicrograph of dilated capillary in corium, showing the granular, fibrillar, and cellular character of the thrombus which is partially occluding its lumen. Note the suggestive protrusion of the basement membrane into the thrombus and the intima-like character of the cells within its substance. *C*, low-power photomicrograph of corium, showing degeneration of collagen fibers adjacent to an occluded capillary.

abnormal bleeding occurred after the first few days. On Dec. 20 a biopsy specimen (Biopsy 3) was obtained from the indurated area of the left thigh. The pathology report reads as follows.

"The section shows a striking increase in the number of small blood vessels most of which seem to be capillaries. Nearly all these vessels are partially or completely occluded [Fig. 3,*A*]. Most of the material within the lumina appears to consist of fibrin strands enmeshing leukocytes but in a few areas the thrombi are made up of a more granular material suggestive of clumped platelets.

"Changes in the vascular walls vary widely. In some places the walls appear normal. In others the subendothelial collagen is more or less thickened, occasionally to such an extent as to protrude small mounds of endothelium into the lumen. The endothelium itself shows some proliferation, especially in a few places where the thrombi are recanalized [Fig. 3,*B*]. There is no inflammatory reaction either in the vessels or peripheral to them. Associated with the occlusion are areas of focal degeneration of collagen and fat [Fig. 3,*C*].

"Diagnosis: Diffuse partial to complete thrombosis of the capillaries of the skin and subcutaneous tissue.

Comment: The histologic pattern strikingly resembles that of thrombotic thrombocytopenic purpura as described by Gore."[1]

However, at that time it was also thought that the patient's condition might be comparable to a giant hemangioma with thrombocytopenia. Two articles on this rare association had appeared a few months previously.[5,6] In one of the cases[5] histologic examination of the hemangioma had shown extensive platelet thromboses similar to those seen in our patient. On the basis of this analogy the consultant radiologist (Dr. O. Wildermuth) recommended radiation therapy. During the next two weeks (Dec. 21 to Jan. 5) 800 r of 220 kv. x-ray therapy was administered to the involved areas on the abdomen and thighs. On Dec. 23 a falling hemoglobin level necessitated one additional transfusion, but thereafter the blood values remained stable and the skin lesions began to heal, and the patient was discharged on Jan. 7, 1956.

The child also received prednisone (Meticorten) in full dosage from Dec. 11 to Jan. 5. The clinical improvement which occurred during this period was probably unrelated, since there was no recurrence of symptoms when the drug was discontinued.

The improvement lasted for nearly a month, during which time no treatment was given. On a follow-up visit on Jan. 17 the platelet count was found to be 99,000 per cubic millimeter. By this time the old skin lesions had almost completely

cleared (Fig. 2, *B*), and, while a few new lesions cropped up now and then, these were small and healed rapidly. However, on Feb. 1, 1956, there suddenly appeared two large purplish-black lesions on the thighs and abdomen. This time the epidermis developed hemorrhagic blebs and part of the underlying tissue formed a black leathery eschar.

Almost constant severe pain and the difficulty of preventing infection of the skin lesions necessitated rehospitalization on Feb. 2, 1956.

Fourth and Final Admission.—Mercy Hospital, Springfield, Ohio, Feb. 2 to 10, 1956.

Laboratory findings on admission were as follows: erythrocytes, 3,750,000 per cubic millimeters; hemoglobin, 9.9 gm.; platelets, 566,000 per cubic millimeter; bleeding time, three minutes; coagulation time, four minutes. Repeat studies on Feb. 9 showed the erythrocyte count decreased to 2,730,000; the hemoglobin, to 8.4 gm. This time plasma electrophoresis gave a nearly normal plasma protein pattern (Fig. 1). New necrotic skin lesions appeared on the thighs. Narcotics were repeatedly needed to control the pain. Death came rather unexpectedly. Soon after a night feeding the nurses found the child looking unaccountably pale and weak. The weakness progressed rapidly, and 10 minutes later the child had died.

A necropsy was performed six hours after death (Dr. M. Hunter). The pertinent findings were reported as follows.

Macroscopic Findings: "When the skin lesions were cut the underlying soft tissues were found to be suffused with blood. The iliac and femoral arteries on both sides were dissected out into their branches as far as fine dissecting scissors would permit but no thrombi were found." The only other grossly diseased organ was the brain. Owing to diffuse edema it was so tightly confined that it was extremely difficult to remove from the skull. Sections showed several small brownish areas irregularly scattered through the white matter.

Microscopic Findings: "In the multiple sections of the soft tissues of the lower abdomen and thighs no thrombi of any kind could be demonstrated by the several pathologists who reviewed the slides. Many sections were made through the hemosiderin-stained areas of the brain. There was evidence of destruction and reparative gliosis but here, too, no evidence of thrombosis was seen in the neighboring vessels." All other organs were essentially normal. (The eyes were not removed for examination.) The immediate cause of death was not evident.

Comment

As the case history indicates, neither the clinical features nor the laboratory studies nor the biopsy or necropsy findings unequivocally established a diagnosis. The following entities were considered and will be discussed below: (*a*) thrombotic thrombocytopenic purpura, (*b*) thrombocytopenic purpura with giant hemangioma, (*c*) vascular (anaphylactoid) purpura, and (*d*) miscellaneous disorders.

(*a*) *Thrombotic Thrombocytopenic Purpura (TTP).*—This is a rare, always fatal, disease characterized by widespread vascular occlusions, hemolytic anemia, and thrombocytopenia. The characteristic histologic picture shows partial or complete occlusions of arterioles and capillaries by an acidophilic homogeneous or finely granular material. Baehr et al.[4] believed that the thrombi consisted entirely of agglutinated platelets. Doubt was thrown on this interpretation when Gore[1] demonstrated that the intraluminal thrombi were often associated and sometimes continuous with subendothelial deposits of a material with the same staining qualities. The exact nature of the acidophilic material remains controversial. There is usually some endothelial proliferation, but signs of inflammation are consistently absent. While the vascular lesions are widely disseminated, their distribution is rarely uniform. Thrombotic lesions may be very extensive in some organs while rare or absent in others. For that reason, biopsies of skin or bone marrow have often failed to show the characteristic lesions.

The clinical symptoms are highly variable. They are the results of the vascular occlusions, of the hemolytic anemia, and of the thrombocytopenia, any of which may dominate the clinical picture at a given time. The central nervous system, where the arterioles are end-arteries, is nearly always affected. Bizarre rapidly changing neurologic phenomena are very characteristic. Nephritis is common; renal and cardiac failure occur occasionally. Major functional impairment of other organs is rare, since there are usually enough intact vessels and anastomoses to prevent infarcts and to carry on function.

Hemolytic anemia is always present at some stage of the illness. It is often the dominant feature. The anemia is apparently not due to a globulin antibody, since the Coombs test is always negative. The hemolytic agent affects both patient and donor cells.[5] Thrombocytopenia is often a transient, sometimes only a terminal, phenomenon; occasionally it is entirely absent. Baehr et al.[4] ascribes the thrombocytopenia to excess consumption of platelets in the thrombotic process. Others have postulated platelet agglutinins, but attempts to demonstrate such antibodies have failed so far.[6,7]

The bone marrow usually shows general hyperplasia. The megakaryocyte-platelet system often appears normal. In other instances the megakaryocytes are increased but show deficient platelet production. This is the so-called "megakaryocyte arrest," first described by Dameshek and Miller[8] for acute idiopathic thrombocytopenic purpura.

The duration of the illness is usually measured in days or weeks; less often, in months or even years. Prolonged remissions occur occasionally. No treatment has proved of value, with the possible exception of splenectomy.[9]

The cause of TTP remains obscure. Some types of allergic or immune reaction has long been suspected on various grounds. The vascular lesions resemble those found in the Shwartzman phenomenon.[10] Many clinical histories contain references to preceding nephritis, rheumatic fever, urticaria, and drug allergies, especially to sulfonamides and penicillin. Whether TTP should be grouped with the collagen diseases seems very doubtful. The vascular lesions of rheumatic fever, polyarteritis nodosa, and temporal arteritis are distinguished histologically by the marked inflammatory changes and clinically by the response to corticosteroids. On the other hand, disseminated lupus erythematosus and TTP seem more closely related and coexist oftener than chance would permit.[11,12] Most authors consider it rather unlikely that there is a single cause for TTP.

Thrombotic thrombocytopenic purpura has been the subject of reviews by Clough (1950),[13] Barondess (1952),[14] Singer (1954),[5] and Adelson et al. (1954).[6] A total of seven cases of TTP in children has been described, three of these in a recent review by Wile and Sturgeon (1956).[15]

Can the illness described above be considered to be TTP? The combination of vascular disorder; variable nonfamilial hemolytic anemia, and intermittent thrombocytopenia at least strongly suggests TTP. But the following points place the diagnosis in doubt.

1. It is difficult to correlate the histologic appearance of the blood vessels with the appearance and evolution of the skin lesions. To recapitulate, the first biopsy specimen showed a subintimal lesion but no thrombus; the second revealed neither vascular degeneration nor luminal obstruction; the third one showed both, and, most disconcertingly, the necropsy showed neither lesion in any of the tissues, contrary to all experiences in TTP. It should be pointed out that all sections were taken from obviously involved skin and subcutaneous tissue. How can these discrepancies be reconciled, and what was the pathogenic mechanism responsible for the lesions? Did the sections of the second biopsy and the necropsy miss the involved portions of the arterioles? Rather unlikely. Or were the occlusions so transient that the thrombi had already been dissolved when the sections were taken? Equally unlikely. Or were the skin lesions not even caused by vascular occlusion but by hemorrhages? Perhaps this is more plausible, since aneurysmal arteriolar changes have been described in TTP.[16]

2. The skin lesions found in our patient are not characteristic for TTP. The usual skin manifestations of TTP are petechiae and ecchymoses, the result of thrombocytopenia. A search of the literature on TTP revealed only a single patient with necrotizing skin lesions resembling those of our patient. This is the case described by Luttgens.[17] The patient was a 20-year-old

woman with TTP, proved by necropsy, who developed on both thighs and one calf ecchymotic areas which soon afterwards became necrotic. The accompanying photographs show these areas to be somewhat similar to the later, severest, lesions of our patient.

3. The hemorrhagic events in TTP are usually adequately explained by the thrombocytopenia. But in our patient the only serious hemorrhagic episode, that of December, 1955, seems to have been due to severe hypofibrinogenemia. Moderate prolongation of the clotting time is occasionally mentioned in other reports, but we have found only two cases with a severer clotting abnormality. Vassar and Spain [18] describe one patient who had a greatly prolonged clotting time, which gradually returned to normal. They offer no explanation for the phenomenon. The second case is the patient of Dickenman et al.,[19] in whom a marked prolongation of the clotting time was a very transient phenomenon, apparently associated with massive thrombus formation in some large arteries and veins. The authors assumed from indirect evidence that the prolonged clotting time was probably due to hypofibrinogenemia. They felt that overconsumption of fibrinogen in the extensive clotting process was the likeliest explanation.

In our patient the extreme reduction of fibrinogen during the hemorrhagic episode was actually demonstrated by plasma electrophoresis (Fig. 1,*B*). There are two possible explanations for the finding. Fibrinogen overconsumption is consistent with the extensive intravascular clotting seen in the biopsy specimen (Fig. 2,*A*). On the other hand, the finding of a proteolytic enzyme in the serum points toward fibrinolysis as the cause. It is conceivable that both factors were involved. To our knowledge, a fibrinolysis has not previously been described in TTP. Its presence should not be surprising in a disease characterized by other autoantibodies, such as hemolysins and possibly antiplatelet and antiendothelial immune bodies.

Another factor may have been a contributing cause. Stephanini et al.[20] recently reported the discovery of antifibrinolysin in platelets. They believe that the reduced blood level of antifibrinolysin in severe thrombocytopenias may be an important factor causing abnormal bleeding in a variety of conditions.

If our patient actually had TTP, the appearance of the first skin lesions at the age of 7 weeks represents the earliest onset on record. The next youngest are Case 2 of Wile and Sturgeon,[15] which started at about 9 months of age, and the patient from St. Christopher's Hospital, Philadelphia,[21] with an onset at 20 months. The description of the congenital eye lesions fits in better with prenatal intraocular hemorrhage than with a developmental anomaly. It is tempting to speculate whether there was a causal relationship between the onset of the child's illness and the mother's sulfonamide-treated pleurisy during the seventh month of pregnancy.

(*b*) *Thrombocytopenic Purpura Associated with Giant Hemangioma.*—The strange association of infantile hemangioma, hemorrhage into and around the tumor, and thrombocytopenic purpura was first described in 1940 by Kasabach and Merritt.[22] Good et al.[2] have recently reviewed 10 cases, including 3 of their own. Biopsies in all of their cases showed extensive platelet thromboses in many capillaries of the hemangiomas, reminiscent of the findings in TTP, though it is stressed that no thromboses were ever found outside the tumor. The bone marrow showed the megakaryocyte "left shift" or "arrest." Platelet antibodies were not found in the one case in which they were looked for.[23] Good et al. concluded that splenectomy had no effect and that the thrombocytopenia subsided only when the hemangioma was removed or its growth was checked by irradiation or spontaneous involution. They attributed the thrombocytopenia to excessive destruction of platelets within the hemangioma. On the other hand, Meeks et al.[3] found in their

case rapid recovery from the thrombocytopenia and regression of the hemangioma after splenectomy. Since both views are documented by convincing case histories, one can only conclude that the syndrome can be produced by different mechanisms.

The histologic appearance of the specimen of Biopsy 3 in our case fitted the description of the hemangioma by Good et al. Furthermore, at the time of this biopsy the bleeding into the subcutaneous abdominal lesions was associated with thrombocytopenia. But in retrospect the resemblance of this syndrome to our case seems rather superficial. No hemangioma was ever actually demonstrated, and at other periods of the patient's illness there was no apparent correlation between the severity of the thrombocytopenia and the extent of the hemorrhagic lesions.

(*c*) *Vascular Purpura.*—Allergic, vascular, and Schönlein-Henoch purpura are different names for what is now considered a single entity.[24] The clotting mechanism is intact, and the platelets are normal in number and quality. The bleeding is due to scattered capillary lesions which seem to have an allergic basis. The vascular purpuras are frequently associated with other allergic phenomena, such as urticaria and rheumatoid joint pains. They often show recurrent cycles of activity and remission. They usually respond well to corticotropin or corticosteroids.

Some sort of allergic or immune reaction seems to be involved in vascular purpura, in idiopathic thrombocytopenic purpura (ITP), and in TTP, and these diseases may have more in common than has been formerly thought.[24] In vascular purpura the reaction is directed against capillary endothelium[25]; in ITP the principal antibodies are platelet agglutinins, though in many cases an accompanying hemolytic anemia and undue capillary fragility suggest the additional presence of hemolysins and antiendothelial immune bodies; in TTP the findings (see above) suggest a hemolytic, antiplatelet, and antiendothelial process but the nature of the immune reaction seems to be different.

The negligible histopathological changes in the blood vessels of our case would fit the diagnosis of vascular purpura, while the recurrent anemia, the failure to respond to corticosteroids, and the fatal outcome favor the diagnosis of TTP.

(*d*) *Miscellaneous Disorders.*—In a search of the literature for rare disorders resembling that of our patient the following possibly related conditions were encountered.

1. Febrile relapsing panniculitis (Weber-Christian). The commoner benign chronic form is easily distinguished, but in rare cases the course is malignant. In such cases the disease may be acute; there may be anemia (usually associated with leukopenia), and, finally, the blood vessels in the nodules may show intimal proliferation and fibrinoid degeneration of the wall.[26] However, biopsies show degeneration of fat tissue with a highly cellular, inflammatory tissue response, easily distinguished from the picture in TTP or in our patient.

2. In 1955 Gardner and Diamond[27] published a study of four patients, under Form of Purpura Producing Painful Bruises Following Autosensitization to Red the title "Autoerythrocyte Sensitization: A Blood Cells in Certain Women." Their patients, all adults, had suffered extensive extravasation at the site of initial trauma. That incident seemed to sensitize them to extravasated blood. For many years thereafter trauma not only produced extensive painful ecchymoses at the site of injury but also seemed to cause various hemorrhages at distant sites. Immunologic studies indicated that these patients had become sensitized to erythrocyte stroma. Platelet counts and other hematologic values were normal. Histologic studies were not reported.

The description of these painful bruises recalls the exquisitely painful purpuric lesions in our patient, but since no comparable studies on erythrocyte sensitization

were carried out on our patient, we cannot tell whether this factor may have been involved.

3. Probably more closely related to our patient is the case of a 36-year-old woman reported by Jernigan and Farber[28] as "Panniculitis with Hemorrhagic Necrosis and Pancytopenia." One of her skin lesions occurred on the forearm; another one, on one leg, but the remainder, as in our patient, on abdomen, thighs, and buttocks. In a skin biopsy specimen "intimal proliferation but no thrombi were seen." Initially the lesions seemed to respond to corticosteroids, but later they were found to be resistant. At present, six years after the onset, the patient is in good health but still develops new lesions.[29]

Leukopenia was not encountered in our patient, but in other respects the resemblance is striking. Again, the available information seems too scant to warrant any conclusions concerning a common etiology.

Summary and Conclusions

The case is described of an infant who suffered from a fatal illness characterized by recurrent painful subcutaneous hemorrhagic lesions, intermittent hemolytic anemia, thrombocytopenia, and transient hypofibrinogenemia.

Neither the clinical course nor the hematologic findings nor repeated biopsies, nor the necropsy established a satisfactory diagnosis.

The following conditions have been considered in the differential diagnosis: thrombotic thrombocytopenic purpura, thrombocytopenic purpura with giant hemangioma, vascular purpura, atypical forms of Weber-Christian disease, autoerythrocyte sensitization, and the panniculitis with hemorrhagic necrosis of Jernigan and Farber.

None of these conditions adequately fitted the picture of our patient, and the possibility must be considered that the child's illness represents a new disease entity.

Yellow Springs Clinic.

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Congenital Atresia of the Inferior Vena Cava, Common Iliac Veins, and Left Innominate Vein

A Case with Extensive Development of Superficial Venous Collateral Circulation

KENNETH F. SWAIMAN, M.D.; SOL AUSTRIAN, M.D., and RICHARD B. RAILE, M.D., Minneapolis

Introduction

Venous anomalies with formation of superficial channels of collateral circulation are rather infrequently encountered. Congenital venous anomalies necessitating intricate superficial collateral systems are even less common.

The purpose of this paper is to present a brief summary of the embryology and medical literature relating to malformations of the primitive cardinal venous system, which lead to the establishment of such collateral systems.

Submitted for publication Jan. 20, 1958.

From the Department of Pediatrics, Minneapolis General Hospital, and the Department of Pediatrics of the University of Minnesota.

In particular, a case of unique venous pattern is presented. We are unable to find documentation of a similar type of case in the literature.

Embryology

As clearly pointed out by Randlett, Jones, and Gardner,[1] the inferior vena cava and its immediate tributaries are formed from a symmetrical system of three paired cardinal veins (Fig. 1,*A*). The left common iliac vein is formed from the iliac postcardinal anastomosis. The right common iliac is formed from the inferior portion of the right postcardinal vein.

The inferior vena cava is composed of four parts. The hepatic portion is formed

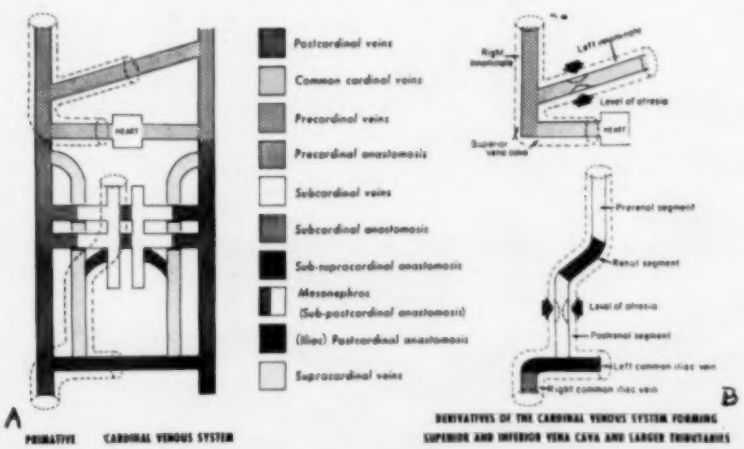


Fig. 1.—*A*, diagrammatic representation of primitive cardinal system before differentiation. Dotted outlines represent sections utilized in formation of superior vena cava, inferior vena cava, and larger tributaries. *B*, diagrammatic representation of derivatives of the cardinal venous system forming superior vena cava, inferior vena cava, and larger tributaries. Diagram demonstrates derivation of each segment as well as areas of atresia (Modified from Randlett et al.[1]).

from the right vitelline vein and the hepatic sinusoids.[2] The remainder of the vessel is formed from the right-sided components of the primitive cardinal system. The prerenal portion is derived from the right subcardinal; the renal portion, from the remnants of the old sub-supracardinal anastomosis, and the postrenal segment, from the right supracardinal vein.

The superior vena cava is formed from the right common cardinal and the inferior portion of the right precardinal vein.[2] The remaining right precardinal vein gives rise to the right innominate vein and the right internal jugular vein. The left innominate vein is created from the formation of a precardinal anastomosis. A portion of the left precardinal vein persists as the left internal jugular. The subclavian and external jugular vessels develop independently and later attach to this system.

Possibilities of Collateral Circulation

Certainly the possibilities of circulation to circumvent a nonfunctioning area of the inferior vena cava are exceedingly numerous. Pleasants, in 1911,[3] in an extensive article on the subject, listed almost all of the reasonable routes of circulation. In his detailed listings he failed to list any collateral system compensating for inferior vena cava absence which involves the veins of the head and neck. He made mention of a system which runs from the superficial inferior epigastric vein, superficial long thoracoepigastric veins, long thoracic veins, axillary vein, and subclavian vein to the innominate vein and thence into the superior vena cava.

Atresia of one of the major veins of the thorax could also lead to a complex system of venous collateral. Specifically, atresia of an innominate vein would lead to rerouting of the venous flow through those smaller distal vessels which have communication with the other half of the body. Such a system would possibly include the thyroid veins, anterior jugular veins, external and internal jugular veins, anterior and posterior facial veins, posterior auricular veins, and the mass of veins which connect over the midline in the occipital area.[4]

One would assume that a superficial system would be unnecessary and would not form if a functioning deep system utilizing the derivatives of the cardinal system was functional and was capable of conducting the large volume of blood presented to it.

Review of Published Cases

Pleasants[3] stated that there had been eight cases of congenital obstruction of the inferior vena cava reported previous to his article and added one more case. He clearly stated, "It is very questionable, however, whether all of these cases are truly congenital in origin." Apparently none of the cases were diagnosed in childhood, and, indeed, only two of these cases came to autopsy. One case was in a 54-year-old man who had no signs of collateral circulation until the age of 52.

The other case was that of an 18-year-old patient who died from erysipelas. At autopsy the upper portion of the inferior vena cava at the level of the diaphragm and the superior vena cava above the entrance of the great azygos vein were obliterated. All venous return was through the azygos circulation.

The possibility exists that none of these cases was truly congenital in origin but that thrombosis with secondary obliteration of the inferior vena cava took place.

No mention is made of involvement of the head or neck vessels in any of these cases. Angelman, Hall, and Spencer, in 1950,[5] reported three cases of obstruction of the inferior vena cava in childhood. In each case signs of collateral circulation were noted well beyond the neonatal period, and the earliest diagnosis of collateral circulation was made at the age of 15 months. This child subsequently died, and on postmortem examination the entire inferior vena cava, both renal veins, the left lateral sinus, and some branches of the pulmonary arteries were found to be thrombosed.

Fig. 2.—Picture taken a week after birth. Note large superficial veins.

The other two cases developed symptoms after acute episodes of illness (i. e., rubeola and severe diarrhea).

In 1957 Edwards and Bennett [6] reported a case of an infant they first saw at 16 days of age who had dilated veins of the abdomen. By means of angiography they concluded that their patient had hypoplasia or atresia of the postrenal segment of the inferior vena cava and common iliac veins. They felt that the entire picture was related to maldevelopment of the right supracardinal vein and the right postcardinal vein.

Report of a Case

On Nov. 17, 1956, at Minneapolis General Hospital, a Negro boy was born; low outlet forceps were used. He breathed and cried immediately. Birth weight was 3540 gm. The attending obstetrician noted large dilated veins over the abdomen (Fig. 2) and requested that the baby be seen immediately by the pediatric house staff.

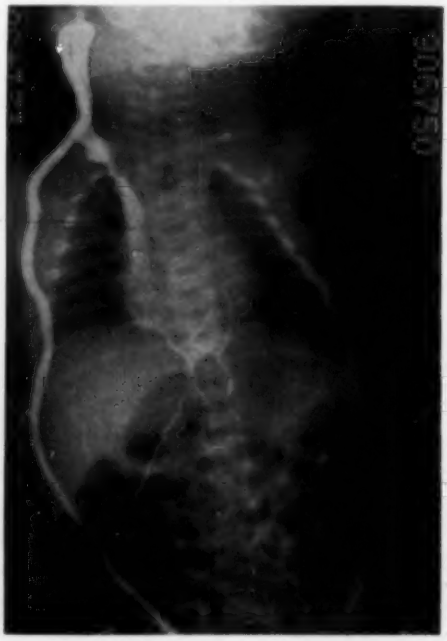
Examination of the baby revealed the presence of cutis laxis and scrotal edema with a right hydrocele.

The most remarkable finding, however, was the presence of large veins 1 cm. in diameter originating near the umbilicus and coursing up the right abdomen and chest, from there leading up the right neck, then forming a huge venous plexus behind and below the right ear. There was a smaller vein originating near the umbilicus on the left of the abdomen which communicated with the larger right-sided system over the right thorax.

The veins appeared to fill from below. Examination of the heart was totally unremarkable. The liver was palpable 1 cm. below the right costal margin; the spleen was not palpable.

There was no edema of the extremities, nor were there dilated veins over the extremities. The femoral pulses were present, strong, and equal. Flush blood pressures revealed the systolic pressure in both arms to be 80 and in both legs to be

Fig. 3.—Angiocardiogram demonstrating course of venous return from right leg.



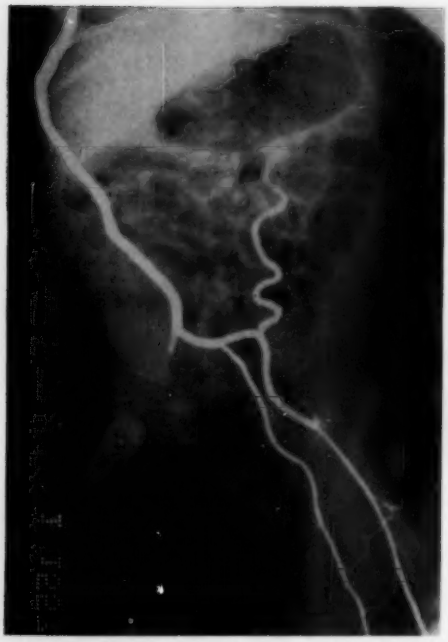


Fig. 4.—Angiocardiogram demonstrating course of venous return from left leg.

100. The impression of the initial examiner was that this obvious superficial collateral circulation was secondary to "inadequate inferior vena cava drainage with poor compensation of the azygos system."

Chest x-rays on the first day of life were read as normal. An electrocardiogram on the same day was within normal limits.

The laboratory tests revealed a normal hemogram. Renal-function and liver-function tests were normal.

Cardiac fluoroscopy proved to be unremarkable. The barium swallow revealed no varices of the esophagus and no enlargement of the left atrium. An intravenous pyelogram demonstrated normal function and position of the kidneys. Contrast medium was injected through a cut-down incision over the lower right greater saphenous vein. Roentgenograms (Fig. 3) revealed that the dye traversed the saphenous vein and then appeared in the subcutaneous abdominal veins and flowed through this system up behind the right ear and then appeared to empty via the superior vena cava into the right atrium.

The baby continued to gain weight and behaved normally. After a short time, contrast medium was injected into the inferior portion of the left greater saphenous vein, and again the contrast material flowed up to the superficial abdominal and thoracic veins, to the right postauricular area (Fig. 4) and appeared to empty into the right atrium via the superior vena cava.

An attempt to catheterize the inferior vena cava in retrograde fashion by reaching the right atrium through the vessels of the left arm and thorax was unsuccessful. The catheter was passed to an area coinciding with the left innominate vein but could not be advanced into the superior vena cava. Contrast medium was then injected at this point of obstruction, and the results were followed with cineangiography. The dye traversed the catheter to a point near the superior vena cava and then coursed its way over many small subcutaneous channels to the venous system over the right neck (Fig. 5A and 5B), then to the right postauricular area, and then subsequently emptied, as before,

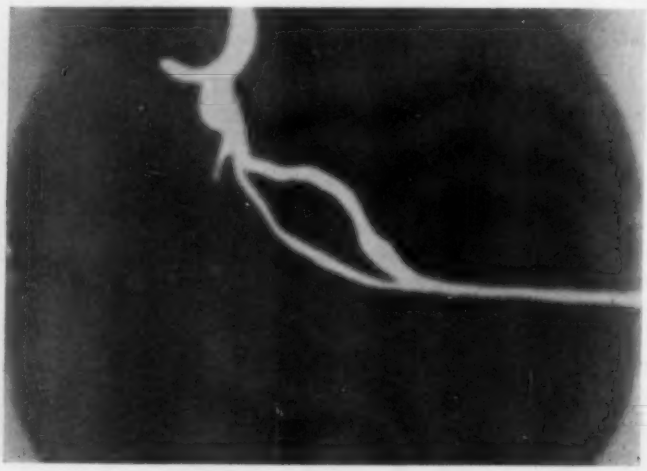


Fig. 5A.—Course of venous return outlined by means of dye injected via a catheter passed through vein of left arm (cineangiogram).

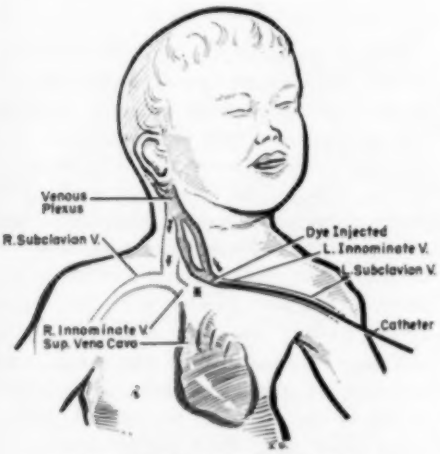


Fig. 5B.—Drawing illustrating position of catheter and anatomical relationships of vascular pattern depicted in cineangiogram (Figure 5A).

through the superior vena cava into the right atrium.

After a period of time, angiography was employed to follow the course of dye injected into a vein of the right arm. The dye emptied normally (Fig. 6) through the axillary, subclavian, innominate, and superior vena cava vessels into the heart. Catheterization was technically impossible through the veins of the right arm because of their small caliber.

At one year of age the child weighs 11.5 kg. He has been in good health, with no complications from his vascular anomaly. He stands without help and otherwise appears to be reasonably normal in motor development.

During the first year venous systems over the back, left neck, and occipital area became pronounced. The circulation over the back of the head is very pronounced, with a rather extensive area of venous plexus, palpable and visible. The flow appears to be from left to right.

Comment

The evidence that we have at hand leads us to believe that our patient has two areas of atresia in his greater venous system (Fig. 1,*B*). There appears to be a defect in the postrenal segment of the inferior vena cava and the common iliac veins. It would appear that if the inferior vena cava were not involved adequate collateral without the superficial venous drainage could be established. It would be reasonable to expect that the upper three segments of the inferior vena cava are normal, for a number of reasons. The intravenous pyelogram revealed good kidney function as well as normal position of both kidneys; hepatic-function and other renal-function tests are normal, and the primitive veins from which these segments arise differ from those (Fig. 1*A* involved with formation of the common iliacs and the postrenal segment of the inferior vena cava. It is also of importance that the precursor of the postrenal portion of the inferior vena cava is formed later than the primitive veins which give rise to the superior three segments. The other vascular defect resides in the failure of the left innominate vein to empty into the superior vena cava. This anomaly necessitates that the left side of the trunk and head be drained by the right internal jugular vein, right innominate vein, and superior vena cava after the blood is transported by way

Fig. 6.—Angiocardiogram demonstrating normal course of venous return from right arm.

of the small anterior and posterior veins to the large venous channels apparent in the right postauricular area.

The normal angiogram obtained after injection of the vein of the right arm demonstrates that the right axillary, subclavian, and innominate veins are present and functioning normally.

As mentioned previously, the defects postulated in this infant would stem from maldevelopment of the right supracardinal vein and also of the precardinal anastomosis. It is to be noted that both these vessels are formed sometime during the seventh week of gestation.[2]

Treatment

This anomalous venous system poses two rather serious problems. As the patient grows and assumes the upright position, eventually this superficial venous system will be forced to support a column of blood 5 or 6 ft. in height. The absence of valves in these vessels will permit massive pooling of blood in the vessels of the legs and lower trunk, with probable formation of varicosities and edema. In addition, the superficial exposure of these large veins makes traumatic rupture or laceration a potential threat to life.

Superficially, it would appear that surgical correction of the defects in the left innominate vein and inferior vena cava would be feasible. However, our surgical consultants feel that the technical difficulties which hamper anastomosis of large veins, as well as the likelihood of providing a mechanical by-pass during the procedure, make the success of this operation rather doubtful at this time. Perhaps greater advances over our present state of knowledge will enable surgical correction to be performed in the future.

Summary

Malformations of the primitive cardinal system which necessitate formation of superficial venous channels are very unusual. The inferior vena cava is formed from the right-sided cardinal veins as well as the right vitelline vein and the hepatic sinusoids. The superior vena cava and the innominate veins are formed from the superior portion of the cardinal system. Congenital atresia of the inferior vena cava appears to be well documented in only one previous case.

A case is presented in which numerous angiographic studies reveal the apparent atresia of the postrenal segment of the inferior vena cava, the common iliac veins, and the left innominate vein. This combination of defects led to formation of an extensive superficial collateral circulation involving the abdomen, chest, back, neck, and posterior head. We believe that no similar case has been reported.

Department of Pediatrics, University of Minnesota Medical School (14).

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Abstracts from Current Literature

Editorial Note

In this issue, abstracts of Russian papers of interest to pediatricians are published. The Excerpta Medica Foundation, with support from the United States Public Health Service, publishes a journal known as *Abstracts of Soviet Medicine*. This journal is published quarterly, contains 175 to 200 pages, and covers all fields of medicine. Since the section on pediatrics is extensive, we have selected for republication those abstracts which seem to be of special interest. The American address of The Excerpta Medica Foundation is New York Academy of Medicine Building, 2 E. 103d St., New York 29. Subscriptions to the *Abstracts* are $15 per year for Section A (Medical Sciences) and $15 per year for Section B (Clinical Medicine—from which these abstracts are taken), or $25 for both.

In addition, we are publishing an extensive news item in this issue about the Pergamon Institute, which is also devoted to bringing the work of Russian scientists to the attention of non-Russian-speaking people. This Institute provides a service whereby complete translations of Russian articles may be obtained at a cost which "will be shared equally with others requesting the article."

The reaction of our readers to the Russian abstracts is invited.

R. L. D.

American Heart Journal, St. Louis

Abstracted by Edward C. Matthews, M.D.

55, No. 2 (Feb.) 1958

* Cyanotic Congenital Heart Disease in One of Identical Twins: Report of Two Cases. Yusuf Ziya Yuceoglu and David T. Dresdale.—p. 255.

Cor Triatriatum. Paul W. Seavey and Edward R. Dorney.—p. 272.

Hemodynamic Complications in Tetralogy of Fallot After Pulmonary Valvectomy of Infundibulectomy (Brock Procedure). T. K. Lin, Antoni M. Diehl, and C. Frederick Kittle.—p. 288.

The Structure of the Renal Glomerulus. C. Barber Mueller.—p. 304.

Cyanotic Congenital Heart Disease in One of Identical Twins: Report of Two Cases.

Two instances of congenital heart disease occurring in one of identical twins are reported, and the factors known to produce congenital heart disease are reviewed.

One pair of twins were 9-year-old girls, one of whom had a pentalogy of Fallot, and the second pair were 9-year-old boys, one of whom had tetralogy of Fallot. The corresponding twin in each case had no evidence of congenital heart disease. The diagnosis of the anatomic cardiac defect was established in each instance by cardiac catheterization and angiocardiography.

The monozygoticity of the twins was established by the "similarity method," said to be about 98% accurate, coupled with identical blood types. It was noted that the finger prints of the respective twins were not identical, a feature to be anticipated in identical twins. While finger prints in identical twins are usually similar, they are never identical.

The genesis of congenital cardiac defects, in general, is poorly understood. It becomes even more difficult to explain the occurrence of a congenital cardiac defect in one of monovular twins. The genetic constitution of monovular twins must be identical, and, at least in theory, the twins are exposed to the same environment during their intrauterine existence.

The causes of congenital cardiac defects may be divided into the general groups of heredity and/or environment. Pointing to a hereditary genesis for congenital cardiac defects are observations and studies by a number of investigators which show that the incidence of congenital heart disease among descendants of a family with congenital heart disease is commoner than would be expected by chance, and there is some evidence that consanguinity may be associated with a higher incidence of congenital cardiac defects.

A number of environmental factors have been shown to play a role in the causation of congenital heart disease either in man or in the experimental animal. Maternal rubella is a well-established cause of congenital cardiac defects. Other factors affecting the pregnant mother which may lead to congenital cardiac defects include radiation, cortisone therapy, toxoplasmosis, poisoning, trauma, and various nutritional deficiencies. Congenital cardiac defects have been produced by the injection of the pregnant animal with trypan blue or azo dyes. Age of the mother seems to be a factor—congenital defects being commoner in children of mothers under 20 years and over 35 years than in those between these two age groups.

It is difficult to implicate any of the known causes of congenital heart disease as being causative in the production of a congenital cardiac lesion in one of monovular twins, but it would seem most likely that an environmental factor might lead to an abnormality of one twin while not affecting the other.

American Journal of Medicine, New York

Abstracted by Hugo Dunlap Smith, M.D.

23, No. 3 (Sept.) 1957

Potassium Movement in Normal Subjects: Effect on Muscle Function. David Grob, Ake Liljestrand, and Richard J. Johns.—p. 340.

Potassium Movement in Patients with Familial Periodic Paralysis: Relationship to the Defect in Muscle Function. David Grob, Richard J. Johns, and Ake Liljestrand.—p. 356.

* Adynamia Episcodica Hereditaria: A Disease Clinically Resembling Familial Periodic Paralysis but Characterized by Increasing Serum Potassium During the Paralytic Attacks. I. Gamstorp, M. Hauge, H. F. Helweg-Larsen, H. Mjönes, and U. Sagild.—p. 385.

Potassium Deficiency of Renal and Adrenal Origin. R. V. Brooks, R. R. McSwiney, F. T. G. Prunty, and F. J. Y. Wood.—p. 391.

Marfan's Syndrome: A Report of Three Patients with Aneurysm of the Aorta. Elias G. Pappas, Daniel Mason, and Clarence Denton.—p. 426.

Marfan's Syndrome: Description of a Family. Rodman Wilson.—p. 434.

Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma). Gerald P. Rodman, George E. Schreiner, and Roger L. Black.—p. 445.

* "Periodic Fever": Occurrence in Five Generations. Bertha A. Bouroncle and Charles A. Doan.—p. 502.

23, No. 4 (Oct.) 1957

* Acute Nephritis Unrelated to Group A Hemolytic Streptococcus Infection: Report of Ten Cases. Richard A. Bates, Robert B. Jennings, and David P. Earle.—p. 510.

Treatment of Renal Failure with Disposable Artificial Kidney: Results in Fifty-Two Patients. Shigeto Aoyama and William J. Kolff.—p. 565.

* Characteristics of Leukocytes in the Urine Sediment in Pyelonephritis: Correlation with Renal Biopsies. K. Peter Poirier and George Gee Jackson.—p. 579.

Salt and Water Volume Receptors: An Exercise in Physiologic Apologetics. Homer W. Smith.—p. 623.

23, No. 5 (Nov.) 1957

Thrombotic Thrombocytopenic Purpura: A Report of Three Cases. J. George Sharnoff.—p. 740.

* The Appearance of New Cardiac Murmurs in Patients Having Rheumatic Heart Disease with No Concomitant Evidence of Rheumatic Activity. T. N. Harris, Sidney Friedman, and James Tang.—p. 748.

"Cor Triatriatum." C. Glenn Sawyer, Robert S. Pool, Walter C. Beck, and Louis B. Daniel Jr.—p. 798.

Hageman Trait (Hageman Factor Deficiency). Robert T. S. Jim and Sam Goldfein.—p. 824.

Post-Transfusion Thrombocytopenic Purpura. Francis W. Michel.—p. 838.

Adynamia Episodica Hereditaria: A Disease Clinically Resembling Familial Periodic Paralysis but Characterized by Increasing Serum Potassium During the Paralytic Attacks.—Gamstorp et al. report on a dominantly inherited disorder that has afflicted 138 members of two Scandinavian families. The illness, called adynamica episodica hereditaria, usually is first manifested in childhood and is characterized by recurrent attacks of paralysis which begin shortly following exercise. Attacks also may be provoked by the oral administration of potassium. The attacks begin with a feeling of heaviness in the limbs and then proceed to paralysis of varying severity, rarely complete—oftenest in the legs and arms, commonly in the face and muscles of articulation, and rarely in the respiratory muscles. During an attack the tendon reflexes are commonly absent or hypoactive and the Chvostek sign may become positive, but otherwise the neurologic examination is normal. The serum potassium rises transiently during most attacks and is accompanied by electrocardiographic and electromyographic changes. To explain this rise, a shift in

body potassium from the cells is assumed, since urinary excretion, as a rule, is increased during the attack and premedication with glucose can inhibit the provoking effect of the oral potassium salts. Intravenously administered calcium will curtail the symptoms of an attack. To date there have been no deaths from this disorder, and histologic examination of muscle tissue from four patients has shown no pathologic changes.

"Periodic Fever": Occurrence in Five Generations.—Although many view the concept of periodic disease with skepticism, the report of Bouroncle and Doan is of interest. They studied three persons in a family in which members of five generations are known to have been afflicted by recurrent 3- to 5-day episodes of fever, occurring usually every 21 to 28 days from early childhood on. During the febrile episodes, general malaise, constipation, arthralgia, and chills were common complaints. Except for irregular circular areas of redness over the trunk, the physical examination during the attacks was normal. No bacteriologic, immunologic, hematologic, or radiographic abnormalities could be demonstrated other than a mild increase in α_2-globulin and β-globulin. The etiology of this disorder is not understood, although the authors feel that allergic, psychogenic, infectious, and endocrinologic causes have been excluded. Cortisone therapy during the attacks of fever was beneficial in improving the symptoms in two patients and in suppressing or markedly ameliorating attacks in a third.

Acute Nephritis Unrelated to Group A Hemolytic Streptococcus Infection: Report of Ten Cases.—Bates, Jennings, and Earle describe an unusual epidemic of acute hemorrhagic nephritis among young naval recruits. Although the nephritis followed an acute pharyngitis, bacteriologic and serologic studies excluded the presence of Group A hemolytic streptococci in 9 of the 10 patients and the latent period between the pharyngitis and the nephritis was less than five days long. Compared with 11 patients who developed acute glomerulonephritis following Group A streptococcic infection, these patients had more prolonged hematuria, briefer proteinuria, and almost no edema, hypertension, or azotemia. Renal biopsies did not reveal the hypercellularity, inflammatory-cell infiltration, and basement membrane changes seen in classical poststreptococcic nephritis but instead only showed evidence in some of the glomeruli of red blood cells and protein precipitate in Bowman's space—rather mild and focal changes. Arteries, arterioles, and tubules were all believed to be normal. The prognosis in these patients appears to be excellent, although microscopic hematuria persisted in 8 of the 10 patients for the duration of the study (between 55 and 162 days).

Characteristics of Leukocytes in the Urine Sediment in Pyelonephritis: Correlation with Renal Biopsies.—In an attempt to improve the early diagnosis of pyelonephritis, Poirier and Jackson studied urinary sediments for "granular motility cells" or "glitter cells." They found that the presence or absence of granular motility in the cytoplasm of pale-staining leukocytes depended upon the composition and osmolarity of the urine and did not reflect activity of pyelonephritis. In contrast, in patients with pyelonephritis (proved by renal biopsy) pale-staining leukocytes were always found when repeated urinalyses were performed and were found in 66% when only a single random urinalysis was obtained. By studies with use of supravital staining of venous blood and of pus from acute inflammation, the authors showed that these pale-staining leukocytes were young cells which with aging changed properties so that staining resulted in dark cells. Therefore, the presence of these pale-staining cells in the urine would suggest active infection, a finding of particular significance in the early stages of pyelonephritis, when the concentrating power of the kidney may still allow for urine of high specific gravity in which granular motility of the pale cells will not be seen.

The Appearance of New Cardiac Murmurs in Patients Having Rheumatic Heart Disease with No Concomitant Evidence of Rheumatic Activity.—It has long been known that patients who have previously had rheumatic fever may develop new organic heart murmurs at times when there is no gross clinical manifestation of rheumatic activity. Harris, Friedman, and Tang report on four patients who developed new murmurs of valvular insufficiency while under close medical supervision. Studies before and after the development of the murmurs revealed that no elevation in sedimentation rate, C-reactive protein, mucoprotein tyrosine, ASO titer, or antihyaluronidase titer occurred at the time the new murmurs developed. Realizing that 13 to 85 months had elapsed between the last

clinical evidence of rheumatic activity and the development of the new murmurs and that Aschoff bodies may be found frequently upon auricular biopsy in patients lacking evidence of activity of their rheumatic process, the authors conclude that the development of these new murmurs was evidence of activity of the rheumatic process. Furthermore, since two of the four patients had been maintained on penicillin prophylaxis prior to the development of the new murmurs, it is speculated that this activity had not developed *de novo* but rather that subclinical activity had persisted from the time of the acute episode of rheumatic fever. In two other patients with questionable laboratory evidence of rheumatic activity the development of cardiac enlargement was believed to be evidence of such activity.

American Journal of Pathology

Abstracted by Jay Bernstein, M.D.

33, No. 6 (Nov.-Dec.) 1957

Morphologic and Functional Changes Associated with Transplantable ACTH-Producing Pituitary Tumors of Mice. Robert Bahn, Jacob Furth, Evelyn Anderson, and Evelyn Gadsden.—p. 1075.

Influence of Subcutaneously Administered Bovine Globulin on the Response of Rabbits to Intravenous Gram-Negative Endotoxin or Liquoid. Peter E. Fehr and Joel G. Brunson.—p. 1193.

Cytopathologic Changes in Tissue Cultures of Human Amnionic Cells Infected with Poliomyelitis, Coxsackie, and ECHO Viruses. H. Bernkopf and A. Rosin.—p. 1215.

34, No. 1 (Jan.-Feb.) 1958

* The Composition of the LE and Hematoxylin Bodies of Systemic Lupus Erythematosus. Gabriel C. Godman, Arline D. Deitch, and Paul Klemperer.—p. 1.

Malformations Caused by Necrosis in the Embryo, Illustrated by the Effect of Selenium Compounds in Chick Embryos. Peter Gruenwald.—p. 77.

The Effect of Various Diabetogenic Hormones on the Structure of the Rabbit Pancreas. Bruno W. Volk and Sydney S. Ladarus.—p. 121.

Adrenal Changes in Post-Term Infants and the Placental Dysfunction Syndrome. Robert P. Bolande.—p. 137.

The Association of Vascular Anomalies with Anencephaly: A Post-Mortem Study of Nine Cases in One of Which Unilateral Anencephaly was Present in a Conjoined Double Monster. Stephen F. Vogel.—p. 169.

The Composition of the LE and Hematoxylin Bodies of Systemic Lupus Erythematosus.—A relative decrease of staining with methyl green, a nuclear stain specific for polymerized DNA, in the hematoxylin-staining bodies of lupus erythematosus has suggested that the bodies are depolymerized DNA. However, acetylation to block competing basic groups of protein prior to staining leads to increased binding of the bodies with methyl green. And, the Feulgen-methyl green ratio approaches unity, suggesting that the initial extinction of methyl green staining was due to protein interference rather than depolymerization of the DNA. Comparison of lymphocyte nuclei and free L. E. bodies showed greater staining with naphthol yellow S, a stain indicating available basic protein groups, and a more intense Millon reaction for tyrosine residues of protein in the latter. A simultaneous decrease in stainable histone groups suggested that in the formation of L. E. bodies a protein not usually present in nuclei displaces histone from its combination with DNA. It is the foreign protein which seems to interfere with methyl green staining, and there is no cytochemical evidence to indicate that the L. E. phenomenon primarily alters the DNA.

American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Springfield, Ill.

Abstracted by Donald H. Altman, M.D.

78 (July) 1957

Fluoride Osteosclerosis. Clyde A. Stevenson and A. Ralph Watson.—p. 13.

* Idiopathic Hypercalcemia. J. A. Shiers, E. B. D. Neuhauser, and J. R. Bowman.—p. 19.

Idiopathic Hypercalcemia.—Idiopathic hypercalcemia was first reported in 1952 by Fanconi and Schlesinger. They reported idiopathic hypercalcemia associated with osteosclerosis, azotemia, retarded development, and congenital malformations. Since that time, five further cases have been reported, one of which was a cretin, and this article deals with four additional cases, including one cretin.

Each case is summarized in some detail. The essential clinical features consist of (1) those manifestations directly due to the raised serum calcium levels, i. e., marked muscular

weakness and hypertonia, anorexia, vomiting, constipation, and failure to thrive, and (2) those due to changes in organs damaged by prolonged hypocalcemia, i. e., marked retardation of growth which could result in permanent dwarfing if the patient lives long enough, toxic effects of calcium on the central nervous system resulting in mental retardation progressing to mental deficiency, and toxic effects of calcium on the kidney producing renal damage and on the heart resulting in extensive damage to the endocardium and myocardium.

In addition to the direct and indirect manifestations of hypercalcemia, certain findings are apparent which are apparently without relationship to the high serum calcium levels. These symptoms suggest that the syndrome may be a genetically determined inborn abnormality involving, among other defects, an error of calcium metabolism. Several of these cases have had a facies described as "elfin," with prominent eyes, often Mongoloid lids, hypertelorism, big mouths, small pointed heads, receding foreheads and chins, and large low-set ears.

The radiographic findings consisted of widespread osteosclerosis, evidence of defective bone formation, and abnormal soft tissue calcifications. The osteosclerotic changes are not distributed evenly but occur in bands or zones which shade off gradually into bone of normal or even diminished density, as if the intensity of the disease varies at different stages of growth. Undertubulation of bone and retarded bone development were features of almost all cases.

The disease is indistinguishable clinically from renal acidosis except for the marked hypotonia. In this condition the persistent alkaline urine and low serum alkali reserve should clarify the diagnosis. The clinical appearance makes it very hard to distinguish these patients from cretins. Radiographically it may be impossible to distinguish the bone changes from those of osteopetrosis (Albers-Schönberg disease). The clinical picture, however, easily helps to differentiate these two conditions. The clinical and roentgen findings may simulate those of hypervitaminosis D. Other conditions causing widespread increase in bone density, such as leukemia; syphilis; lead, phosphorus, and fluorine poisoning; hypervitaminosis A, Hodgkin's disease, or physiological osteosclerosis of the newborn, should be differentiated clinically.

The clinical and radiographic changes in these cases are identical to those produced by excessive doses of vitamin D. Although, according to standards of normal, the intake of vitamin D was not excessive, poisoning cannot be altogether ruled out. Some of these patients have been reported to have become worse after small doses of vitamin D or even after exposure to sunlight. There are grounds for believing that requirements for vitamin D vary greatly from one person to another, and it has been suggested that these patients represent those who are excessively sensitive to even small doses of vitamin D. This hypersensitivity may be on a genetic basis.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

77, No. 1 (Jan.) 1958

Experiences with Bronchography Using 3,5-Diiodo-4-Pyridone N-Acetic Acid (Dionosil). Charles T. Pinney, Daniel E. Wertman, and Billie B. Streete.—p. 32.

* Endobronchial Tuberculosis in Children: A Study of 156 Patients. Edith M. Lincoln, Leonard C. Harris, Somchai Bovornkitti, and Rosario W. Carretero.—p. 39.

The Effect of Diet on the Inducement of Acquired Resistance by Viable and Nonviable Vaccines in Experimental Tuberculosis. Lloyd W. Hedgecock.—p. 93.

Protein and Nucleic Acid in Caseous Necrosis. Kendal C. Dixon.—p. 106.

Serum Protein Changes in Experimental Tuberculosis. Ben C. Sher, Alvin Dubin, Yosh Takimura, J. de la Huerga, and Hans Popper.—p. 120.

Effect of Tween 80 and Serum on the Interaction of Mycobacteriophage D-29 with Certain Mycobacterial Species. Arthur White and Vernon Knight.—p. 134.

Studies on the Catalase Enzyme of Mycobacteria: I. Correlation Between Catalase Activity and Virulence of Mycobacteria Under Certain Experimental Conditions. Ottó Schweiger, Elvira Román and I. Soós.—p. 146.

Possible Superinfection with Isoniazid-Resistant Tubercle Bacilli. Achyut G. Motiwale and Emanuel Wolinsky.—p. 168.

Endobronchial Tuberculosis in Children: A Study of 156 Patients.—A group of 156 children with primary tuberculosis showing endoscopic evidence of bronchial tuberculosis is reported. In this series of cases, endobronchial tuberculosis was more frequent in children less than 4 years of age, and in boys. Severe symptoms were more often observed in young infants.

Roentgenographic evidence of obstruction was observed in 90% of the patients. Evidence of segmental obstruction was more commonly seen in the right lung and most often seen in the right middle lobe and in the anterior segment of the right upper lobe. Seventy-seven per cent of the group received antimicrobial therapy; in sixty-six per cent of those who were treated, the medication was given for more than six months; in forty-eight per cent, for more than a year.

Granulation tissue was the most frequent finding on bronchoscopy. There were polypsin 54 of the 156 patients, and erosion of the bronchial wall was diagnosed in 25 cases. The duration of endobronchial involvement by bronchoscopy could be measured in only 70 patients. It continued for less than three months in 11 children, 4 of whom were untreated; from one to more than three years in 23 children, 18 of whom received specific therapy, and for more than a year in 10 children.

Bronchograms were done in 103 cases without selection and showed abnormal findings in 70 and marked abnormalities in 50. Bronchiectasis was the commonest evidence of damage, occurring in 70% of those with marked abnormalities. The percentages of children with abnormal bronchograms were very similar in the treated and untreated groups.

There is no evidence that antimicrobial therapy markedly shortens the course of tuberculous endobronchitis due to encroachment of caseous nodes on bronchi. There is also no evidence that the use of specific therapy diminishes the incidence of sequelae in bronchi and parenchyma. Nevertheless, there is justification for treating children with tuberculous endobronchitis in the hope of diminishing the dangers of bronchogenic spread of the tuberculous.

Annals of Internal Medicine, Lancaster, Pa.

Abstracted by Brian Kiely, M.D.

46, No. 3 (March) 1957

* The Neurologic Manifestations of the Acute Leukemias: A Clinical Study. Charles E. Wells and Richard T. Silver.—p. 439.

A Thrombasthenia Syndrome Associated with Hyperheparinemia. Warren N. Bell and Irving Imber.—p. 537.

Editorial: The Responsibilities of the Medical Profession in the Use of X-Rays and Other Ionizing Radiation. Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation.—p. 638.

The Neurologic Manifestations of the Acute Leukemias: A Clinical Study.—Neurologic manifestations were looked for in 63 patients (29 children and 34 adults) with proved acute leukemia admitted to the National Cancer Institute and were found in 24 cases. There was no relationship of their incidence to the cell type or age. The commonest neurologic complication was intracranial hemorrhage, which occurred in 12 patients, most of whom had very low platelet counts. In 11 cases neurologic signs were attributed to leukemic infiltration, although, as has been noted by others, the pathologic findings often appeared inadequate to explain the clinical findings. In this group the latter included evidence of increased intracranial pressure, impairment of consciousness, convulsions, meningismus, pleocytosis, pyramidal tract signs, involvement of the basal ganglia and hypothalamus, and cranial and peripheral nerve pareses. Seven patients improved neurologically on treatment with 6-mercaptopurine, Methotrexate, and cortisone although two of them showed no hematologic response. In one case the neurological manifestations occurred while the patient was in hematologic remission but responded to treatment nevertheless.

One patient developed bacterial meningitis due to Staphylococcus pyogenes var. aureus. Of four patients classed as miscellaneous, two had psychoses, one of which was due to cortisone.

British Medical Journal, London

Abstracted by Hugo M. Cardullo, M.D.

1, No. 5062 (Jan. 11) 1958

* Fatty Liver of Endocrine Origin: With Special Reference to Fatty Liver of Malnourished African Infants. J. Gillman and C. Gilbert.—p. 57.

* Further Studies on the Transmission of Staph. Aureus. Ronald Hare and Mark Ridley.—p. 69.
* Acquisition of Staph. Aureus by Newborn Babies in a Hospital Maternity Department. J. Cook, J. A. Parrish, and R. A. Shooter.—p. 74.
* Masking and Gowning in Nurseries for the Newborn Infant: Effect on Staphylococcal Carriage and Infection. J. O. Forfar and A. F. Maccabe.—p. 76.

Fatty Liver of Endocrine Origin: With Special Reference to Fatty Liver of Malnourished African Infants.—Fatty liver is one of the constant features of African infants suffering from pellagra and kwashiorkor. A mildly fatty liver containing approximately 8% of total lipids early in the illness may evolve into one containing over 40% of total lipids within nine days. Such a rapid evolution of the fatty change suggested that the acute episode in infants was the result of a sudden metabolic disorder occurring against a background of chronic malnutrition. This view implies that there are two stages in the natural history of florid kwashiorkor and infantile pellagra. The first, determined by chronic malnutrition, is initiated before or shortly after weaning. No fatty liver develops during this stage, but the reactivity of the infant is altered, with the result that a mild intercurrent infection, a sudden change in temperature, or a mild gastrointestinal upset may precipitate the second stage, which declares itself as florid kwashiorkor or as infantile pellagra. During the second stage a fatty liver develops rapidly.

Fatty liver has been produced consistently in the baboon by various endocrine techniques. Irrespective of the way a particular hormone altered metabolism, a fatty liver did not emerge unless insulin was relatively or absolutely insufficient and an adequate amount of adrenocortical hormone was available. It was demonstrated that in defined circumstances thyroxin could promote the resolution of a fatty liver.

It is suggested that the acutely developing fatty liver of malnourished African infants might be related to an acute endocrine disturbance involving the islets of Langerhans, the adrenal cortex, and the thyroid gland and not necessarily to atrophy of the exocrine part of the pancreas.

Further Studies on the Transmission of Staph. Aureus.—Extensive surveys of the skin and clothing of nasal carriers of Staphylococcus pyogenes var. aureus have shown that about three-fifths have sufficient numbers of this organism on certain areas, particularly the hands and the clothing of the front of the body, to enable them to transmit their own organisms to other persons with whom they come into direct physical contact, by means of objects such as blankets or towels which they have touched, or as a result of dispersal into free air during movement.

With many carriers, the primary source of these organisms is the nose, but the number of S. pyogenes var. aureus organisms in the nasal swabs gives little indication of the extent of skin and clothing contamination or ability to disperse this organism. Nevertheless, at least one person in the series studied in this paper had a primary source which was not in the nose but on the skin of the perineum. S. pyogenes var. aureus from this area could contaminate the skin and clothing and be dispersed during the movement to much the same extent as with nasal carriers.

Thus, when possible sources of infection are being sought, the existence of non-nasal carriers of S. pyogenes var. aureus must not be overlooked.

Acquisition of Staph. Aureus by Newborn Babies in a Hospital Maternity Department.—An investigation among full-term newborn babies in two nurseries has been carried out in an attempt to discover the usual routes of spread of Staphylococcus pyogenes var. aureus.

Initially 53 babies were all found to be nasal carriers by the 10th day and 11 of 12 of these babies also carried staphylococci in their stools. Examination of bedding suggested that this was not the immediate source of staphylococci, and prevention of possible contamination from the staff by the use of Chlorhexidine hand cream or gowns made little difference.

The use of triple dye on the umbilicus and individual gowns for each baby, both as separate and as combined measures, produced a reduction in the nasal carriage rate on the 12th day of life by about 25% to 30%.

No evidence was obtained that babies gained staphylococci from their mothers, but there was evidence that staphylococci on the mothers' breasts came from their babies.

Masking and Gowning in Nurseries for the Newborn Infant: Effect on the Staphylococcal Carriage and Infection.—A controlled experiment was carried out in a maternity unit to determine the effectiveness of masking and gowning in reducing the staphylococcal infection of and carriage on newborn babies. A strict masking and gowning regimen was employed in one nursery but not in another.

In both nurseries the same proportion of infants suffered from minor staphylococcal infections. The sites of occurrence of these infections were the eye and skin predominantly and also the umbilicus. Between the two nurseries there was no significant difference as to site of infection.

The carriage rate for staphylococci in the babies in the two nurseries was determined by examining swabs from the eye, nose, and umbilicus. The carriage rate for staphylococci in the attendant nursing personnel was determined by nasal swabbing. There was no significant difference in the carriage rates for babies in the masked and unmasked nurseries or between the babies and the attendant personnel.

There was no significant difference in the drug sensitivity pattern of staphylococci isolated from babies in the two nurseries, but there was a significant difference in pattern between babies' and nurses' staphylococci.

It is concluded that direct transfer of staphylococci from the nose and mouth of attendant personnel to the baby is not an important means of infection of the latter and that masking and gowning in maternity nurseries is unlikely, therefore, to be an effective preventive measure.

Journal of the American Medical Association

Abstracted by Don Hosier, M.D.

166, No. 5 (Feb. 1) 1958

Choriocarcinoma in Mother and Infant. R. O. Mercer, A. C. Lammert, Robin Anderson, and J. B. Hazard.—p. 482.

Pediatric Surgery Is Growing Up. W. J. Potts.—p. 462.

166, No. 6 (Feb. 8) 1958

* Hyaline Membrane Syndrome. C. C. Chapple.—p. 619.

The Significance of Pulmonary Hyaline Membranes in Newborn Infants. Peter Gruenwald.—p. 621.

Hyaline Membrane Syndrome.—The clinical signs of hyaline membrane syndrome can simulate the respiratory difficulties seen in any one of a variety of abnormal states. Most of the cases of this hyaline-membrane-like condition occur in one of three general categories: infants born (1) prematurely, (2) of diabetic mothers, and (3) by cesarean section. In the author's opinion, in each of these situations the mothers could be expected to have levels of circulating hormones which might induce an increased permeability of the pulmonary capillaries in their offspring. Progesterone makes cells electrically less responsive and more chemically open, i. e., under its influence their membranes tend to permit transmission of liquids.

For the babies of diabetic mothers the first definite specific therapeutic measure for hyaline membrane syndrome is discussed. It has been shown that in babies of diabetic mothers the arterial blood has shown evidence of severe respiratory acidosis. Administration of a solution of 5% glucose and 0.45 gm. per 100 cc. of saline is begun at 1 oz. per pound per day shortly after birth. The arterial pCO_2 in all but one infant treated in this manner returned to normal within the first 24 hours.

Journal of Pediatrics, St. Louis

Abstracted by Demetrius G. Traggis, M.D.

51, No. 6 (Dec.) 1957

The Roentgenographic Findings Associated with Neuroblastoma. C. F. Hansman and B. R. Girdany.—p. 621.

Urinary Excretion of Fluoride by Children Aged Two Through Five Years Using a Stannous Fluoride-Containing Dentifrice in a Natural Fluoride Area and a Nonfluoride Area. R. A. Schweinsberger and J. C. Muhler.—p. 634.

* Interstitial Plasma Cell Pneumonia and Pneumocystis Carinii. A. Ariztia, W. Bustamante, L. Moreno, A. Doberti, C. Roman, T. Pizzi, and M. Diaz.—p. 639.

Comparison of Ocular Reactions Using Penicillin and Bacitracin Ointments in Ophthalmia Neonatorum Prophylaxis. A. M. Margileth.—p. 646.

Formation of Mucous Membrane Lesions Secondary to Prolonged Use of One Percent Aqueous Gentian Violet. E. L. Slotkowski.—p. 652.

Novobiocin in Common Pediatric Infections. A. D. Gerguson, G. C. Teixeira, and R. B. Scott.—p. 655.
Apparent Sensitization to Novobiocin. J. G. Hughes.—p. 664.
The Roentgenographic Diagnosis of Geophagia (Dirt-Eating) in Children. J. E. Gardner and F. Tevetoglu.—p. 667.
Ear Studies in the Newborn Infant. M. S. McLellan and C. H. Webb.—p. 672.
Growth and Development: I. Relation of Birth Weight in Negro Infants to Sex, Maternal Age, Parity, Prenatal Care, and Socioeconomic Status. E. P. Crump, C. P. Horton, J. Masuoka, and D. Ryan.—p. 678.
Surgical Treatment of Pyloric Stenosis in an Infant with Hemophilia. J. I. de Bruijne, S. van Creveld, and R. Steendijk.—p. 698.
Sporadic Cretinism with Goiter Occurring in Identical Twins. H. F. Frierson, J. C. Hawk, and M. Q. Jenkins.—p. 704.
Infant and Child Mortality in a Korean Rural Area. D. J. Yun.—p. 709.
The Children's Medical Center, Boston, Mass.—p. 716.
Hyaline Membrane Disease. Paul Curtis.—p. 726.
Natural Immunity to Poliomyelitis. R. J. Blattner.—p. 742.

Interstitial Plasma Cell Pneumonia and Pneumocystis Carinii.—The authors report on the first 10 cases in Chile of interstitial plasma-cell pneumonia in which Pneumoncystis carinii was present. The authors review the literature, pointing out the following: The disease is a severe respiratory one, usually attacking premature and undernourished infants; pathological findings show widespread interstitial infiltration of the lungs with mononuclear cells and plasmocytes and a peculiar foamy exudate in the alveoli; many cases appear as epidemics in hospital wards; the etiology has not been definitely proved, although in most cases a parasite, Pneumoncystis carinii, known to infect a wide variety of animals, has been found in the lungs; very few cases have been reported in the Americas, most cases being in central and northern European countries.

The following clinical picture was found in their cases: There were seven cases in premature infants, two in full-term infants, and one birth weight was unknown; onset was between 3 and 6 months of age; all infants were undernourished; onset was often mild and nonspecific, but in six cases onset was with increasing dyspnea, cyanosis, and loss of appetite; in four cases onset was sudden; fever was moderate, and temperature was never higher than 38 C. Physical examination revealed marked discrepancy between dyspnea and physical signs: Percussion was usually negative (one had hyperresonance); in four auscultation was negative, and in six moderate crepitations and rales were noted; duration of disease in two was less than one week; in three, about two weeks; in five, more than two weeks; laboratory studies were negative. X-ray may be characteristic: severe, persistent interstitial emphysema that flattens and immobolizes diaphragm; bulging of intercostal spaces; mediastinal emphysema (or encroachment on the mediastinum by emphysematous lung). Parenchymal findings vary from nothing to micronodular infiltration to peribronchial infiltration, lobar or segmentary; emphysema appears early and lasts a long time; treatment with various antibiotics and cortisone did not seem to help. Anatomical findings were as described by others, the authors recommending that histological samples should be taken from the deeper and darker lung zones. The parasites may be seen in sections and in smears, mainly in the foamy exudate in the alveoli; their average diameter is 1μ to 3μ; they often appear in rosette-like structures.

In their discussion the authors point out the similarity of the clinical and laboratory findings in their cases to those of the other cases reported. The striking features are the scarcity of physical signs associated with severe functional and systematic involvement, the high mortality rate, the typical pathological findings, the finding of the sporozoon-like parasite in the foamy alveoli exudate, and the epidemic character affecting almost exclusively premature and/or undernourished infants. The differential diagnosis includes different types of viral pneumonia, bacterial bronchopneumonia, bronchiolitis, and foreign bodies. The authors report that a complement-deviation test, with use of an antigen or extract of lungs of infants who have died, may be helpful. The authors also report that, in spite of the presence of the parasite, neither it nor any other agent has been definitely proved to be the cause of the disease.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

52, No. 38, 1957

[a] Cipron in Child Psychiatry. A. Mahr.—p. 1670.
[a] Immunobiology and Clinic of Fetal Erythroblastosis: Part I. G. Hörmann.—p. 1672.

52, No. 39, 1957

*Immunobiology and Clinic of Fetal Erythroblastosis: Part II. G. Hormann and Schmukell.—p. 1714.

52, No. 43, 1957

Organic Disorders as Causes of Difficulty in Education: I. Endocrinopathies. G. Destunis.—p. 1867.

52, No. 44, 1957

Organic Disorders as Causes of Difficulty in Education: II. Mechanical Injury and Anoxia of the Brain, Encephalitis. G. Destunis.—p. 1905.

The Simultaneous Administration of Tetanus Immune Serum and Tetanus Toxoid Vaccination in Cases of Fresh Wounds. F. Huber.—p. 1919.

52, No. 45, 1957

* Problems of Cardiovascular Complications After Smallpox Vaccination. E. Lyon.—p. 1947.

Oxygen Therapy with Hydrogen Peroxide. W. Wagner.—p. 1956.

* The Treatment of Psoriasis. J. Stefl.—p. 1967.

Goiter of School Age Children in the Vicinity of Berlin and Its Treatment in Practice. P. Habermann.—p. 1992.

53, No. 3 (Jan. 17) 1958

* Treatment of Multiple Pyoderma in Infancy with Oxytetracycline. W. Sommerfeld.—p. 107.

53, No. 4 (Jan. 24) 1958

* Variability of Infectious Hepatitis in Children. V. Kredba.—p. 136.

* A Little-Known Localization of the Enanthem in Rubeola. Z. Maretic and I. Matijasic.—p. 145.

Cipron in Child Psychiatry.—Cipron is a meprobamate preparation in tablet form containing 200 mg. Depending on the age, the daily dosage is 1 tablet t. i. d. to 2 tablets t. i. d. Side-effects were noted in a few cases. The treatment was given in cases of absences, petit mal, psychic manifestations with symptoms of enuresis, encoprosis, tic, severe general motor unrest, lability, attacks of rages, general debility, speech disturbances, and voluntary suppression of speech or of eating, with or without changes in the EEG. In a number of cases, often with increased cerebral irritability evident in the EEG, lying, stealing, and other behavior disturbances were noted.

In some of these cases the psychotherapeutic measures were considerably aided by the medication.

Immunobiology and Clinic of Fetal Erythroblastosis: Part I and Part II.—The two papers represent a review of the problem of erythroblastosis fetalis, with a list of 234 references.

Problems of Cardiovascular Complications After Smallpox Vaccination.—Even if rarely, it seems that injury of the myocardium can also occur in children following vaccination against smallpox. As a rule, it is a slight transitory complication.

The Treatment of Psoriasis.—Good results are reported from the treatment of psoriasis with racemic lactic acid administered as such or in foods such as acid milk, sauerkraut, and others. Twenty drops of a 20% lactic acid solution was given t. i. d. by mouth. The levortatory isomere is not effective.

Treatment of Multiple Pyoderma in Infancy with Oxytetracycline.—Fifty-nine infants ranging in age from 9 days to 10 months were treated with 10 mg. of oxytetracycline (Terramycin) per kilogram every six hours for multiple pyoderma due to hemolytic Staphylococcus pyogenes var. aureus. When the lesions discharged pus spontaneously or by incision, in some cases, potassium permanganate baths were given in addition. The average duration of treatment was 11 days to recovery. In control series treated in the usual manner recovery resulted in 20 days on the average, in 51 of 60 cases. Number and consistency of the stools did not change, and no overgrowth of Candida albicans was noted. No allergic side-effects occurred.

Variability of Infectious Hepatitis in Children.—On the basis of 11,322 own cases the following forms of infectious hepatitis are described: (1) an abortive form, which differs from the (6) anicteric form inasmuch as a slight preicteric phase and an icterus of sclerae and soft palate of short duration occur; (2) a mild form; (3) a moderately severe form;

(4) a severe form, and (5) a protracted form. As previously reported by the author, infectious hepatitis is rare during the first years of life (0.4%) but is usually severe. The symptomatology of the preicteric phase is tabulated, comprising 1000 cases in each age group of 1 to 5 years, 6 to 8 years, and 12 to 13 years. In another table the symptomatology of three most prevalent forms; abortive, light, and moderately severe is registered, and in another table, the distribution of the various forms among the different age groups. Furthermore, their distribution with reference to the preepidemic period and to the beginning and to the height of the epidemic period is listed, as well as the incidence of the various groups during different years. The greater number of moderately severe, severe, and protracted cases fall into the 12- to 13-year-old group (13.4%). At the start of an epidemic more of the severe forms are seen than at its peak. The abortive form is credited with a considerably greater number of cases than the anicteric form.

A Little-Known Localization of the Enanthem in Rubeola.—A 25-year-old nurse developed appendicitis during an attack of rubeola. At laparotomy a pronounced enanthem of the parietal and visceral peritoneum was seen.

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

257, No. 18 (Oct. 31) 1957

Primary Varicella Pneumonia. S. Krugman, C. H. Goodrich, and R. Ward.—p. 843.

An Evaluation of the Respiratory and Sedative Effects of Meperidine Hydrochloride Combined with Levallorphan Tartrate in Postoperative Patients. R. Megirian and C. W. White.—p. 849.

Inhibitory Effect of Perthane (2,2-Bis-[Paraethylphenyl]-1,1-Dichloroethane) on Adrenocortical Function in Human Subjects. I. Taliaferro and L. Leone.—p. 855.

* A Study of Intercurrent Bacterial Respiratory Infections in Bulbospinal Poliomyelitis. J. B. Livingstone, F. K. Austen, and L. J. Kunz.—p. 861.

Labor's Interest in Medical Care. N. H. Cruikshank.—p. 866.

Giant Ovarian Cyst: Report of a Case in a Premature Infant. W. H. Brune, E. J. Pulaski, and H. E. Shuey. —p. 876.

257, No. 19 (Nov. 7) 1957

Radiation Hazards: III. Radiation Protection in Diagnostic Procedures. L. L. Robbins.—p. 922.

257, No. 22 (Nov. 28) 1957

Zinc Metabolism in Hepatic Dysfunction: II. Correlation of Metabolic Patterns with Biochemical Findings. B. L. Vallee, W. E. C. Wacker, A. F. Bartholomay, and F. L. Hoch.—p. 1055.

Clinical Implications of Isoniazid Blood Levels in Pulmonary Tuberculosis. R. S. Mitchell and J. C. Bell.—p. 1066.

Clinical Experiences with a New Carbonic Anhydrase Inhibitor as an Oral Diuretic. I. Hirshleifer, N. Shaftel, and D. J. Behr.—p. 1074.

Metabolism and Toxicity of Ammonia. W. V. McDermott Jr.—p. 1076.

A Study of Intercurrent Bacterial Respiratory Infections in Bulbospinal Poliomyelitis. The authors state that, in their experiences, the two major causes of death in bulbospinal poliomyelitis are circulatory collapse and pulmonary infection. They report on a study of the bacterial flora of the trachea after tracheostomy.

Twenty-five consecutive patients who required both a respirator and a tracheostomy were included in the study. Ages ranged from 16 to 58 years. Tracheostomies were done within five days of admission because of inability to handle secretions. In two other cases tracheostomies were done on the 7th and 11th days because of palatal weakness and pneumonia, respectively. Two respirator units with 20 tank respirators in each unit were established; these were then divided into units of 4, with two nurses for each 4. An attempt was made to keep catheters for nasopharyngeal and tracheal suction separate in a sterile towel, but this was not always done. All personnel wore gowns and masks. Initially 15 of the 25 were receiving antibiotics prophylactically; 10 were receiving penicillin and streptomycin; 4, penicillin alone, and 1, tetracycline intravenously and streptomycin. Cultures of the trachea were obtained daily during the first month and three times a week afterward. Specimens were obtained by cotton-tipped flexible wire introduced through tracheostomy tube, from the end of the inner tube immediately after removal, and by bronchoscopy. It was found that culturing the end of the inner tube was as satisfactory as the other two methods. Bacteriological techniques and sensitivity tests were carried out as usual. At 12-day intervals cultures were also

obtained from throats and fingernails of house staff and nurses and from the masks of the tidal-volume and anesthesia machines used by the patients.

Nine different species of bacteria were isolated from 520 specimens of the 25 patients. The four species of bacteria most commonly found were Staphylococcus pyogenes var. aureus, 83%; Pseudomonas aeruginosa, 11% to 5%; Proteus species, 8.9%; β-hemolytic Streptococcus, 4.4%. Staph. pyogenes var. aureus was obtained in pure culture more than one-half of the times it was isolated; Gram-negative bacteria and β-hemolytic Streptococcus were usually mixed with Staph. pyogenes var. aureus. Other bacteria were occasionally found, and negative cultures for aerobic bacteria were obtained only 23 times (4.4%). Nose and throat cultures usually reflected the trachea flora but not vice versa. 89% of the Staph. pyogenes var. aureus showed multiple resistance to antibiotics (usually penicillin, streptomycin, and oxytetracycline). All but one patient had resistant Staph. pyogenes var. aureus, whether or not prophylactic antibiotics were given. In 17 cases a sensitive Staph. pyogenes var. aureus was replaced by a resistant one. The fingernails and throats of the personnel and the masks of the machines all grew out resistant Staph. pyogenes var. aureus consistently. Sixteen of the twenty-five patients developed pulmonary sepsis; in fifteen of these a resistant Staph. pyogenes var. aureus was the predominating organism. Seven of eleven patients who recovered maintained their resistant Staph. pyogenes var. aureus in the trachea.

The authors feel that the resistant Staph. pyogenes var. aureus, acquired by the patients, was a hospital strain, as has been demonstrated before. They point out again that penicillin and streptomycin prophylaxis are of no value. Also, once implanted the organism is often impossible to eradicate with chemotherapy, and the authors advise its use only when sepsis is present. Early choice of antibiotics is governed by the sensitivities of the currently prevalent strain. In the sickest patients, especially those who died, Gram-negative rods often appeared, three of four showing Pseudomonas aeruginosa. The authors suggested the use of polymyxin B. The authors pointed out the value of careful mechanical removal of secretions in the treatment of pulmonary sepsis.

Pediatrics

Abstracted by William W. Cleveland, M.D.

20, No. 5 (Oct.) 1957

Management of the Patient with Cleft Lip and Cleft Palate. Donald W. MacCollum and Sylvia Onesti Richardson.—p. 573.

* Activity of Glutamic-Oxaloacetic Transaminase in the Serum in the Neonatal Period. Simon Kove, Stanley Goldstein, and Felix Wróblewski.—p. 584.

* Measurement of Activity of Transaminases in the Serum as an Aid in Differential Diagnosis of Jaundice in the Neonatal Period. Simon Kove, Stanley Goldstein, and Felix Wróblewski.—p. 590.

Differences of Somatic and Respiratory Response to Hypoxia in Newly Born and Older Infants. Franklin C. Behrle and Ned W. Smull.—p. 601.

Needle Biopsy in Children with Nephrosis: A Study of Glomerular Damage and Effect of Adrenal Steroids. Enrigue Galán and C. Masó.—p. 610.

Corrected Transposition of the Great Vessels of the Heart: A Review of 17 Cases. Ray Anderson, C. Walton Lillehei, and Richard G. Lester.—p. 626.

Experimental Studies on the Pathogenesis of Kernicterus. Lars Ernster, Lennart Herlin, and Rolf Zetterström. —p. 647.

Extensive Cranial Decompression in the Treatment of Severe Lead Encephalopathy. Robert L. McLaurin and James B. Nichols Jr.—p. 653.

Use of Glucose, Invert Sugar and Fructose for Parenteral Feeding of Children. Harold C. Lane and Katherine Dodd.—p. 668.

The Relative Merits of Isoniazid and Other Therapeutic Agents in the Treatment of Tuberculous Meningitis in Children. Bret Ratner, George R. Klimkiewicz, William C. Ellis, H. John Malone, and Joseph Dolgin.—p. 676.

Nontuberculous Acid-Fast Bacilli in Cervical Adenitis. Haddow M. Keith, Lyle A. Weed, and Gerald M. Needham.—p. 688.

Note on the Repair of Cleft Lip at the Twelfth Hour After Birth. William C. Thoroughgood and Carl C. Fischer.—p. 698.

Children with Cerebral Palsy: Cost of Care and Results in 770 Children. Helen M. Wallace, Margaret A. Losty, David Sanders, Robert S. Stiffert, Jerome S. Tobis, and Herbert Rich.—p. 703.

Pediatrics and Society. Samuel M. Wishik.—p. 716.

Utilizing a School for Handicapped Children in Medical Education. Elena Boder.—p. 719.

Activity of Glutamic-Oxaloacetic Transaminase in the Serum in the Neonatal Period.—Results of spectrophotometric determinations of glutamic-oxaloacetic acid transaminase (GOT) activity in 63 normal newly born infants from birth to 11 days of age are reported. This

activity was found to vary from 15 to 105 units, as compared with the range of 5 to 45 units found in normal adults. No relation to age of these young infants was demonstrated, with the exception that cord blood values were, in general, lower than those obtained later. From these data the authors conclude that values of GOT activity up to 120 units by their methods should be considered physiologic for newly born infants. Physiologic icterus in these babies was not found to be associated with increased GOT activity.

Measurement of Activity of Transaminases in the Serum as an Aid in Differential Diagnosis of Jaundice in the Neonatal Period.—Concurrently with the measurement of GOT activity in newborn infants GPT activity was determined in 63 normal infants in the first week of life, and the values are reported to range from 10 to 80 units; as was the case with GOT, no relationship of GPT levels to physiologic hyperbilirubinemia was noted. Measurements of levels of both enzymes were made in infants with erythroblastosis fetalis, and, again, normal values were noted, with the exception of one severely jaundiced infant who had moderate elevation of GOT. With biliary obstruction, however, sustained elevation of enzyme levels was noted for as long as biliary obstruction persisted. The diagnostic value of determinations of GOT and GPT levels in young infants with jaundice is discussed.

Abstracts from the Soviet Literature

A selection of abstracts drawn from the current issue of Abstracts of Soviet Medicine, *a quarterly journal published by the Excerpta Medica Foundation (New York Academy of Medicine Building, 2 E. 103d St., New York 29), with the aid of a grant from the U. S. Public Health Service*

Newborn Period, Prematurity, Embryopathy

Balunova, A. O.: Ob arterialnom krovyanom davlenii u nedonoshennykh detei (*The arterial blood pressure in premature children*) Pediat. Akus. Ginek. 1956, 4 (3-6).

The dynamics of blood pressure in 101 prematures between the ages of 1 day and 3 months were studied. The blood pressure readings showed that the arterial blood pressure is lower in prematures than in full-term children and depends on the degree of prematurity. The low arterial pressure, its great variability, and also the variability of the pulse testify to the inadequacy of functional capacity of the cardiovascular system of prematurely born children, which points to an imperfect regulation of the circulation by the CNS. By taking blood pressure readings one is able to judge the degree of viability of prematurely born children.

Babich, Z. E.: Nekotorye pokazateli obmena u novorozhdennykh, kotorye perenesli asfiksiyu, i u nedonoshennykh (*Data on the metabolism of newborn children who had suffered from asphyxia, and of premature children* [*Ukranian text*]) Pediat. Akus. Ginek. 1956, 4 (7-10).

The glycolytic activity of the blood of newborn children who had suffered from asphyxia was higher than that of healthy full-term infants; in premature children it was still higher. This demonstrates the presence of hypoxia in the newborn children and also the capacity of the organism of the child to utilize the anaerobic carbohydrate metabolism as a source of energy. In children who had suffered from asphyxia, and in premature children, a long-lasting creatinuria was found. The glycolytic activity of the blood and the creatinuria are useful indices of the condition and the development of the newborn.

Krasik, L. B.; Kuznetsova, N. K.; Glikina, R. I.; Voronova, A. N., and Kochetkova, Z. V.: Organizatsiya i rabota otdelenii dlya nedonoshennykh detei v detskikh bolnitsakhg. Molotova (*The organization and work of the departments for premature children in the pediatric hospitals of the town of Molotov*) Vop. Okhr. Mater. Det. 1956, 1/6 (60-64).

An account is given of the work of a hospital for premature children. The principal aim was the fight for the preservation of life and further normal development of the premature child. Premature children weighing from 1000 to 2000 gm. were admitted to the department on the 15th day of life from the maternity home. The regular organization of nursing-care; the early change-over to seven to eight feeds a day, with addition of proteins to the breast milk; the early administration of vitamins, and stimulating therapy enabled the authors to achieve satisfactory results.

Titov, A. I.: Khronaksiya u donoshennykh i nedonoshennykh detei v pervye dni zhizni (*Chronaxy in full-term and premature children during the first days of life*) Pediatriia 1956, 5 (11-13).

It has been ascertained that in healthy newborn children the chronaxy during the first eight days of life is nearly twice that of adults; in healthy premature children the chronaxy is nearly twice that of healthy full-term children, and in premature children with signs of intracranial hemorrhage the chronaxy values were still higher. The author suggests that the study of chronaxy in children can be used for diagnostic purposes in those cases where the clinical picture of intracranial injury is not fully conclusive.

Blood, Hemopoietic System, Blood-Group Antagonism

Probatova, L. E.: K voprosu o lechenii anemii nedonoshennykh detei (*The treatment of anemia in premature children*) Pediatriia 1956, 5(7-11).

In the treatment of anemia in premature children, the author used repeated transfusions of blood and erythrocyte suspensions every two to three days, the observations being made on 50 premature children. The transfusions gave positive results; the hemoglobin level did not fall below 60 to 65 degrees Sahli. In view of the fact that this method of treatment is difficult to use in an outpatient department, the author tested the efficacy of treatment with Haematogen. This was given in the milk, beginning from the second month of life of the premature child, initially 5 drops twice a day and increasing after 7 to 10 days to 10 drops twice a day. In children with a birth weight below 1 kg. Haematogen was started with 2 drops once to twice a day. Seventy premature children were the subjects of observation, the birth weight in 70% of cases being below 1.5 kg. In addition to the Haematogen, the children received a complex of vitamins C, D, and B by mouth. Comparing the two methods of treatment, the author points out that, though with Haematogen the hemoglobin level was, on average, lower than with blood transfusions, the development of the children receiving Haematogen and their adaptability to extrauterine life was better, they gained more weight, and they had fewer illnesses; their illnesses ran a milder course, without toxicosis, and ended with recovery. The treatment with Haematogen spares the child the trauma associated with blood transfusion.

Bubnova, M. N., and Sokolova, K. F., Department of Pediatrics of the Second Medical Institute, Moscow: Vliyanie gormonalnoi terapii na techenie ostryh leikozov u detei (*The influence of hormonal therapy on the course of acute leukaemia in children*) Vop. Pediat. 1957, 1 (26-30).

The effectiveness of hormonal preparations (ACTH and cortisone) was studied in 10 children aged 4 to 14 years with acute leukaemia. The treatment was a complex one and included the organization of the regimen with sufficient daily sleep, good ventilation, high-quality food, vitamins, transfusion of packed red cells, and 300,000 to 400,000 units of penicillin a day. The hormonal preparations were injected i. m. twice a day. Dosages for children of school age were cortisone 100 mg. or ACTH 50 units daily, and for children under school age, cortisone 75 mg. or ACTH 30 units daily. When the blood state began to improve, the dose of the hormonal preparations was reduced by one-third and afterwards by one-half. The course of acute leukemia in children was changed by cortisone and ACTH, which were used in complex therapy, remission being not only clinical but also hematological. Complete clinical remission took place on the 15th to 25th day, but hematological remission occurred somewhat later—on the 25th to 30th day after the beginning of treatment with cortisone. The combined administration of cortisone and ACTH in the complex treatment of acute leukemia in children had the same effect as cortisone alone. However, the improvement was only temporary, and there are only two children alive at the present time. Repeated administration of cortisone in the period of deterioration did not yield any effect.

Chzhun, Shi-Fan, and Chzho, Chzhun-Chan: Anemiya kuli u detei iz provintsii Guandun (*Cooley's anemia in children from the Kwang-tung province*) Pediatriia 1956, 4 (51-56).

Five cases of Cooley's anemia are described, all in natives of the Kwang-tung province. Attention is called to the familial character of Cooley's anemia; while in adults the symptoms and signs of the disease are considerably less marked, and sometimes the disease in them is found out only by careful examination of blood smears, in children Cooley's anemia always runs a grave course and is usually fatal. The causative organism of the disease has not been

found so far. The authors infer that it is some kind of micro-organism which acts on the hemopoietic organs so that they produce unusual, abnormal erythrocytes, which contain an unusual pigment. The erythrocytes disintegrate easily and lose the capacity of absorbing oxygen, and from this anemia results. The patients are usually pale and thin; the liver is enlarged, and at times there are rises of temperature (probably referable to secondary diseases). Microscopical examination of the blood reveals considerable changes in the erythrocytes and a fall in their number; in addition, there are changes in the bones, bone marrow, and internal organs. At present there are no reliable methods of treatment of patients with Cooley's anemia. The authors give a detailed account of the clinical features of one of the observed cases.

Stepanova, K. V.: Khronicheskaya semeinaya gemoliticheskaya anemiya tipa kuli *(Cooley's chronic familial hemolytic anemia)* Pediatriia 1956, 4 (56-60).

A description is given of the clinical picture of the illness of two children (sisters) suffering from Cooley's chronic familial hemolytic anemia. These observations show that Cooley's hemolytic anemia may also be met with in the U. S. S. R. The author presumes that some congenital defect in the activity of the hemopoietic system plays a part in the causation of this anemia. The clinical picture of this type of anemia is characterized by (1) progressive anemia with severe degenerative changes in the erythrocytes, and the presence of a large number of nucleated red blood cells in the peripheral blood as well as in the bone marrow; (2) increased hemolysis, with a characteristic pallor and icteric coloration of the skin and mucous membranes; (3) osteoporosis of the cranial bones together with areas of hypertrophy of bone tissue and thinning of the cortex of the shafts of the long bones together with expansion of the marrow; (4) enlargement of liver and spleen. The course of the disease is undulatory, with rises of temperature depending to a considerable degree on complication by secondary infection. Treatment is symptomatic.

Polyakova, R. P.: Osnovnye zadachi v izuchenii patogeneza, terapii i profilaktiki gemolitich-eskoi bolezni novorozhdennykh (*Main problems of research into the pathogenesis, therapy, and prophylaxis of hemolytic disease of the newborn*) Akus. i Ginek. 1956, 6 (3-11).

In the pathogenesis of hemolytic disease, an important role is played by the functional state of the liver of the newborn; its insufficiency may apparently lead to the development of a severe form of the disease in the child, even where the titer of Rh antibodies in the mother is low. Investigations showed that in the group with Rh incompatibility between mother and child, but no hemolytic disease in the children, the state of the liver was the same as in a group of healthy children. In children with one or another manifestation of hemolytic disease, marked hypoproteinemia, pronounced bilirubinemia, and a high color index of the urine was found; furthermore, there was bilirubin and urobilin in the urine (6 out of 22), which was never found in healthy children. Comparison of clinical and laboratory findings showed that in grave forms of the disease in children with signs of functional insufficiency of the liver the Rh antibody titer in the mother varied, being high in some and medium or low in others. The treatment of hemolytic disease of the newborn consisted in exchange transfusions in which the blood of the newborn, containing Rh antibodies and Rh-positive erythrocytes blocked by them, is replaced by blood of a Rh-negative donor of the same blood group. The mortality among newborn children with severe hemolytic disease treated by the usual small transfusions of Rh-negative blood was 52%, and among those treated by exchange transfusions, 6.5%. The exchange transfusion has to be done before the appearance of manifest clinical signs of the disease, viz., during the first 24 hours of life. Important points for the early diagnosis of hemolytic disease are (1) unfavorable obstetrical history, (2) a high titer of Rh antibodies in the maternal blood, (3) the quantity of bilirubin and hemoglobin in the cord blood, as well as the total number of erythrocytes, and the quantity of hemoglobin and erythroblasts in the peripheral blood. With a view to prevention of hemolytic disease of the newborn, Rh-negative women were given Vikasol (vitamin K), vitamin C, and vitamin E; inhalations of oxygen, and injections of 40% glucose solution, and, in cases of threatening premature labor, progesterone. The measures described lowered the premature birth rate from 49.3% to 11.8% and the stillbirth rate from 37.3% to 7.1%, owing to their increasing the resistance of the fetus against the harmful action of the Rh antibodies; possibly also the permeability of the placenta for antibodies is lowered and the formation of Rh antibodies in inhibited.

Gastrointestinal System

Karadzhi, K. D., Civic Maternity Home, Salavat, S. S. S. R.: Krovotochashchaya yazva dvenadtsatipertstnoi kishki u novorozhdennoi (*Bleeding duodenal ulcer in a newborn*) Sovetsk. Med. 1957, 1 (117).

A case of bleeding duodenal ulcer in a newly born girl is reported. Marked pallor of the integument mucosae followed by copious hemorrhagic feces (five to six motions in 10 hours) developed in this full-term baby within two days after birth. Intestinal hemorrhage was diagnosed. Treatment was ineffectual, and death ensued 11 hours after the onset of symptoms. Autopsy revealed a duodenal ulcer the size of a pea. The mucous and submucous layer of the duodenum was necrotic. An inflammatory reaction surrounded the ulcer. No other pathological changes were found in the gastric or intestinal mucosae.

Respiratory System

Piotrovskaya, S. A., Department of Children's Diseases of the Medical Institute, Vinnitsa: Izmeneniya kharaktera dykhaniya vo vremya bodrstvovaniya i fiziologicheskogo sna u detei, bolnyh pnevmoniei (*Changes in the character of respiration during the period of wakefulness and of physiological sleep in children suffering from pneumonia* [*Ukrainian text*]) Pediat. Akus. Ginek. 1956, 5 (9-14) Illus. 10.

Investigations were carried out on respiratory and blood circulatory function during the period of wakefulness and of physiological sleep in sucklings suffering from pneumonia. The data from pneumography and the blood pressure readings were correlated with the clinical data at different stages of the disease. It was established that pneumonia in sucklings led to a considerable disturbance of rhythm, to increased frequency and amplitude of respiratory movements, and to a fall in blood pressure. The pneumograms showed irregular (at times periodical) respiratory movements, replacement of deep respiratory movements by superficial ones, and sometimes complete apnea of varying duration in cases of pneumonia following a severe course, in cases of its complication with pleurisy or with otitis, and also in the acute stages of the disease. Along with the improvement of the general condition of the patients the respiration became deeper and more rhythmical. A considerable difference in the sensitivity of the respiratory and vasomotor centers was established in the states of wakefulness and of sleep: During physiological sleep the respiratory rate diminished by 10 to 20 movements per minute; the pulse frequency, by 5 to 22 beats per minute; the systolic blood pressure, by 10 to 20 mm. Hg, and the diastolic blood pressure, by 5 to 10 mm. Hg. In sleep induced by the physiological factors of external environment (aeration, application of oxygen), the reduction in the excitability of the cortex led to a reduced frequency and depth of respiration, contributing to better ventilation of the lung tissue and to a decrease in oxygen insufficiency.

Sokolova, K. F.: Sosudistye reaktsii u detei, bolnykh pnevmoniei (*Vasomotor reactions in children suffering from pneumonia*) Vop. Okhr. Mater. Det. 1956, 1/6 (22-28).

The article gives the results of a study of vasomotor reactions in children as indices of the reactivity of the organism. Procedure was as follows: One drop of a 3% carbolic acid solution was applied to the skin of the chest on the right side round the nipple, and another, to the upper third of the right arm. After a few minutes, the fluid was removed, and the temperature was taken with a thermoelement. The temperature was measured before applying the stimulant, and 15 to 30 seconds after its removal, then every minute during the following 10 minutes, every 5 minutes during the next 30 minutes, and, after that, every 10 minutes as long as the temperature did not return to the initial values. The observations were done on two groups of children: (1) 98 children with various forms of pneumonia and (2) 34 healthy small children. The author found a biphasic reaction: a lowering of temperature (vasoconstriction) followed by a rise of temperature (vasodilatation). Comparing the findings, the author points out that in healthy children the vasomotor reactions are lively and strong. In children with pneumonia the vasomotor reactions depend on the severity of the main and accompanying diseases and are much more protracted than in healthy children. At the time of recovery, the vasomotor reactions in the ill children rise to twice the previous level and become higher than in healthy children.

Shiman, E. I., and Shirai, V. Kh.: Piopnevmotoraks u rebenka 1 mesyatsa (*Pyopneumothorax in a child of one month* [*Ukrainian text*]) Pediat. Akus. Ginek. 1956, 5 (34).

A case of pyopneumothorax in a girl of one month is described. Nine pleural punctures were done on the child. Penicillin, streptomycin, and biomycin were given intramuscularly and into the pleural cavity, and, in addition to this, the treatment consisted in blood transfusions and plasma, glucose, vitamins, sulfonamides, calcium chloride, and cardiac stimulants. Full recovery ensued.

Endocrine System

Sapega, A. T., Institute of Obstetrics and Gynaecology, Moscow: Sostoyanie i razvitie detei, rodivshikhsya ot materei, stradayushchikh sakharnym diabetom (*The status and development of children born of diabetic mothers*) Probl. Endokr. 1956, 2/6 (87-89).

Observations were made on 22 children born of mothers with diabetes mellitus. The author concludes that the correct treatment of the mother during pregnancy will ensure a viable fetus. The children were characterized by general apathy, somnolence, and diminution of physiological reflexes. These features gradually disappeared during the early months of infancy.

Shinkerman, N. M.: K patomorfologii zoba u detei v bukovinskom endemichnom ochage (*Pathomorphology of goitre in children residing in the endemic area of Bukovina*) Pediat. Akus. Ginek. 1956, 4 (23-26).

The author investigated the morphology of the thyroid gland in newborn children in the county of Chernovtsy. The thyroid glands of premature children weighed less on the average than those of children born at term. Congenital goiter was found in 3.2% of children up to 1 month old and in 4.4% of children up to 10 days old. Parenchymatous forms comprised 90.9%, and colloid forms, 9.1%; nodular forms were not found.

Acute Infectious Diseases

Ganyushina, E. H., Pediatric Research Institute, Moscow: K voprosu o sovremennom sostoyanii problemy borby so skarlatinoi (*The present position of the problem of combating scarlatina*) Vop. Pediat. 1956, 1/4 (17-23).

An experimental investigation of the higher nervous activity in the light of the teaching of Pavlov revealed a number of disturbances of cortical dynamics in scarlatina and also some changes in the activity of the vegetative nervous system. Thus it revealed the presence of a "sympathetic phase" in the acute period and also a "vagal phase" and an "allergic wave" phase. The author also investigated the effect of prolonged physiological sleep in scarlatina patients. Positive results were obtained; allergic reactions diminished, and phasic phenomena were not observed. The application of penicillin in the form of aerosol inhalation in an amount of 50,000 to 100,000 units twice a day for six days also gave good therapeutic results. Normal temperature was observed in 70% to 85% of patients treated. This made it possible to shorten the period of hospitalization to 14 to 16 days.

Elinson, B. M., Leningrad: "Skarlatinnoe serdtse" po dannym ECG (*"The scarlatinal heart" on the basis of ECG data*) Vop. Pediat. 1956, 1/4 (23-28).

One hundred ninty-four scarlatina patients aged 1 to 13 years were subjected to ECG examination. The three basic leads were registered in all the patients, while in 76 cases the fourth thoracic CR_4 lead was also recorded. Cardiovascular changes were observed in most of the patients, being apparent clinically in 85% of the cases and electrocardiographically in 95%. ECG changes revealed themselves mainly in alterations in the P wave, the QRS complex, the ST interval, and in the T wave in all leads (especially Leads 3 and 4) but also in impaired atrioventricular conductivity. All these findings pointed to an affection of the myocardium of the nature of a myocardiodystrophy and, in some cases, of the character of a focal myocarditis. The cardiovascular changes were more pronounced in older children. ECG changes in scarlatina had a permanent character and were registered in 75% of the patients at the moment of their leaving the clinic. These children must be kept under medical observation until their complete recovery.

Zelentsova, S. S., Department of Pediatrics of the Central Institute for Medical Postgraduate Study, Moscow: Diagnosticheskoe znachenie proby Dick i reaktsii pretsipitatsii pri stertyh formah skarlatiny (*The diagnostic value of the Dick test and of the precipitation reaction in occult forms of scarlatina*) Vop. Pediat. 1956, 1/4 (32-38).

Latent or occult forms of scarlatina constitute a source of dissemination of the infection, since they are extremely difficult to diagnose. One of the reasons of their occurrence, apparently, is the high antitoxic immunity against the background of which the disease develops and because of which the titrated skin test with hemolytic streptococcal toxin is of little diagnostic value. The precipitation reaction was positive in 96% of scarlatina patients and revealed itself as a valuable method in the early diagnosis of the occult and atypical forms of scarlatina. Repeatedly negative reactions in the early stages of the disease alongside with the evaluation of clinical data make it possible to exclude a diagnosis of scarlatina. A positive precipitation reaction in an illness possessing some features in common with scarlatina makes it imperative for the physician to keep the patient in isolation until the appearance of other symptoms of scarlatina.

Sheinman, A. A., Children's Hosp., Zvenigorodka Cherkaski Region: Lechebnaya effektivnost vnutrikozhnoi novokainovoi blokady pri kokluyshe (*Therapeutic effectiveness of intracutaneous Novocain block in whooping-cough*) Pediat. Akus. Ginek. 1956, 6 (32-33).

Intracutaneous Novocain (procaine) block was carried out in 54 children suffering from a severe form of whooping-cough in the stage of spasmodic coughing. A 0.25% to 0.5% solution of Novocain was injected in the area between the centre of the spina scapulae and the second cervical vertebra. In cases of complication with pneumonia the block was carried out along the sides of a rhomboid, the lowest angle of which was at the fourth thoracic vertebra. Only the first injection was felt to be painful by the children. Twenty-one of the children fell asleep during the performance of the block. The amount of Novocain injected varied from 15 to 55 ml., depending on age. The duration of the block was from 15 to 40 minutes. The attacks of convulsive coughing ceased in 70.8% of the children within 10 days following the block; in 20.8% the attacks became milder and less frequent. Considerable improvement took place after a repeat block in 8.4% of the children. The manifestations of pneumonia disappeared on the second to third day after the block. The author recommends the application of intracutaneous Novocain block in the stage of spasmodic coughing in severe cases of whooping-cough.

Maksimovich, N. A.; Kornyushenko, N. P.; Botsman, N. E., and Yatel, T. P., Institute of Infectious Diseases of the U. S. S. R. Academy of Medical Sciences, Kiev: Virusologicheskaya i morfologicheskaya kharakteristika grippoznykh pnevmonii v rannem detskom vozraste (*Virological and morphological characterization of influenzal pneumonias in young children*) Pediat. Akus. Ginek. 1956, 5 (14-21).

A virological and morphological investigation was carried out in the lungs of 34 children who died of pneumonia in the early phase of an influenza outbreak (February-March, 1955). The virus Types A and B were isolated in seven instances. In two cases a viral etiology was established by a positive hemagglutination reaction during the child's lifetime. Posthumous isolation of the virus from the lung tissue was possible mainly in cases where death occurred during the first three to five days of the illness. The bacterial flora was, as a rule, absent in such cases. The hemorrhagic character of pneumonia in influenza described by a number of authors was not macroscopically seen in a single case. The hemorrhagic component was, however, observed in the microscopical investigation of the lungs of children who died during the early days of the illness. The authors draw attention to an acute disturbance of the blood circulation in the lungs, hemorrhages into the lumen of the alveoli and stroma of the lungs, and congestion of the alveolar walls. In the cases of early death there were membranes on the alveolar walls containing protein side by side with the metaplasia of the epithelium of the bronchi, catarrhal bronchitis, and phenomena of the desquamation of the alveolar cells. The presence of the membranes, which disturb the exchange of gases, could contribute to the phenomena of hypoxemia in the child's lifetime. In patients who died at a later stage destructive panbronchitis together with peribronchitis was observed. The exudate filling the bronchi and the alveoli was of various character (purulent, fibrinous, serous). In a number of cases the deposition of bacterial flora that could be seen did not noticeably change the morphological picture characteristic of influenza virus pneumonia.

Bubnova, M. M., and Shcherbatova, E. I.: Vliyanie adrenokortikotropnogo gormona (AKTG) na techenie revmatizma u detei (*The influence of ACTH on the course of rheumatism in children*) Vop. Okhr. Mater. Det. 1956, 1/5 (54-59).

The authors treated 54 children suffering from rheumatism with ACTH (corticotropin) and compared the efficacy of this treatment with the results of Amidopyrine and Butadion treatment of 41 children. ACTH was generally given by i. m. injection, 20 units twice a day, to a total of 1000 to 1320 units for one course. Improvement and disappearance of pathological changes were more rapid in the group of children treated with ACTH than in the group treated with Amidopyrine and Butadion. Less marked was the change in the BSR. In severe forms of rheumatism, and when ACTH was given late, the effect of treatment was less pronounced and the rheumatic process continued to advance. The authors conclude that in cases of severe circulatory failure ACTH is not indicated.

Parasitic, Mycotic Diseases

Zaitseva, G. I., Department of Pediatrics of the Institute for Postgraduate Study, Leningrad: O profilaktike kandidamikoza vnutrennih organov u detei (*Prophylaxis of Candida mycosis of internal organs in children*) Vop. Pediat. 1957, 1 (41-45).

Cases of Candida mycosis of the internal organs have become increasingly more frequent for some time past, especially in children of early age. The disease is connected with the predisposition of children to dystrophic states and to polyhypovitaminosis, and also sometimes with the use of antibiotics. There are a number of conditions which change the reactivity of the child, who is thereby rendered defenseless against Candida albicans. In some cases children are actually born in a state of latent polyhypovitaminosis owing to irrational and unbalanced nutrition of gravidae. It is very necessary, therefore, to ensure high-quality food for pregnant women and not to admit of any restriction therein except on strict medical indications, and even then only for a short time. The administration of supplementary vitamin preparations is necessary. Also important are the nourishment and the supplementary vitaminization of parturient, puerperal, and lactating women. Rational dietetics and vitaminization of children from the earliest days of life, especially during illness, are of great importance. The prevention and early diagnosis of polyhypovitaminosis in children are important factors in the fight against fungal diseases. Antibiotics should be given to pregnant or lactating women only in accordance with strictest indications. The practice of freely giving antibiotics to children "prophylactically" in the early postnatal period is very harmful. Misuse of antibiotics in therapy is a potent factor in the development of Candida mycoses.

Surgery, Roentgenology

Shuvalova, Z. A., Pediatric Surgical Clinic at the Medical Institute, Sverdlovsk: O naibolee ratsionalnom metode lecheniya vypadeniya pryamoi kishki u detei (*A more rational method in treatment of prolapsed rectum in children*) Pediatriia 1956, 6 (56-58).

Dysentery as well as anatomical developmental anomalies plays a leading part in the causation of prolapse of the rectum. The simplest and most favored method of treatment of prolapsed rectum consists in injecting alcohol into the pararectal cellular tissue. The spirit used is 70% proof, and dosage is calculated as 1 ml. of pure spirit per kilogram of body weight. The spirit injections were carried out under ether anesthesia of short duration. One injection was sufficient, in the majority of cases, to prevent further prolapse, while in the remaining cases two to three injections were required. The pathoanatomical changes consist essentially in the formation of connective scarring tissue which assists, to a certain degree, in fixing the rectum to the pelvic wall. Alcohol also penetrates into the blood circulation and increases the muscular tone of the rectum itself and of the muscles holding it.

News and Comment

GENERAL NEWS

Availability of Results of Research and Development in the U. S. S. R. and Other Soviet Orbit Countries in the Field of Science, Technology and Medicine.—Pergamon Institute, a nonprofit foundation, has recently been formed in Washington, D. C., and is in course of formation in London, for the purpose of making available to English-speaking scientists, doctors, and engineers (from all countries that are members of the United Nations) the results of scientific, technological, and medical research and development in the Soviet Union and other countries in the Soviet orbit. The address of the Pergamon Institute is 122 E. 55th St., New York 22. The Joint Presidents of the Institute are Dr. Detlev W. Bronk and Sir Robert Robinson.

The International Council of Scientific Unions, during the recent meeting of its executive Board in Brussels, decided to include a token subvention to the Pergamon Institute in the allocations for 1958, in recognition of the value to international scientific activity of the aims and purpose of the Pergamon Institute.

For the aims and purpose of the Institute, see below.

Over a hundred scientists of international standing from many countries have given their support and will supervise the affairs of the Institute.

The formation and purpose of the Institute were much influenced, among other things, by a report to the United Kingdom Government by its Advisory Council on Scientific Policy, under the chairmanship of Sir Alexander Todd, F.R.S., which, among other things, analyzed the position as follows:

". . . There would, of course, be no problem if Russian were widely read, but our information is that only about 2 per cent of our working scientists can read Russian, compared with 80 to 90 per cent who read French and 60 per cent German. The first thing to be done, therefore, is to encourage the teaching of Russian as an important modern language in schools and universities. . . ." Authoritative sources in the United States also agree that less than 2% of the working scientists in America can read Russian.

Allan T. Waterman, Director of the National Science Foundation, in his recent report to President Eisenhower "Basic Research—A National Resource" said that "recently several American industrial laboratories spent five years and at least $200,000 conducting studies of the design of electrical circuits only to find afterwards that the work had already been done. It was described in a Russian article published in a Soviet journal before the studies started."

He went on to say, "From published Russian sources, it appears that some 24,000 scientists, or about 14 per cent of Soviet scientific manpower, devote their time to basic research. This figure is probably somewhat higher, say between one-fifth and one-third, than the number of scientists—on a full-time equivalent basis—engaged in basic research in the United States. The Soviet Union spent more than 11.6 billion roubles on research and development in 1955, somewhat in excess of 1 per cent of its gross national product, and the proportion that went to basic research is unknown. However, the proportion is presumably less than that based on manpower estimates. These and other facts suggest the following picture:

"1. A remarkably high rate of industrial and technological growth, as indicated by the high rate of increase in gross national product.

"2. An even greater relative increase in research and development as indicated by the increasing ratio of research and development to gross national product.

"3. A country still technologically underdeveloped, as indicated by the low starting level of its research and development—and the low level which still prevails—relative to the United States.

"4. A relatively heavy emphasis on basic research certainly heavy if compared with the United States, but differing from our situation in the authoritarian controls exercised in a dictatorship."

As a result of recently announced scientific and technological developments in the U. S. S. R. there is a great need, as well as pressure from scientists, universities, government departments,

and industrial firms, to overcome the language barrier and to make available rapidly in English the significant results of research and development in the U. S. S. R. in the fields of science, technology, and medicine.

It is one of the primary tasks of the Pergamon Institute to fill this need quickly by the initiation of large-scale translation programs of complete journals and books, as well as individual papers, in all the critical fields of science, technology, and medicine.

Institute Projects.—The following are the projects which have already been started or are being planned by the Institute in association with and with the financial assistance of various Government departments, learned societies, and private organizations and some of the services which are available:

1. It is planned to hold a Symposium during the summer of 1958 either in Washington or in London, sponsored by the Institute and several interested Universities, to examine the following problems: (*a*) how to assist with the establishment of extracurricular courses for the teaching of Russian in the science, medical, and engineering faculties at higher seats of learning in the English-speaking world; (*b*) how to teach the reading of Russian scientific and technical texts to scientists and technologists in the minimum amount of time; (*c*) what tools of learning are required.

2. Discussions are taking place with the relevant authorities in the U. S. S. R. on the commissioning of a series of review volumes, with complete bibliographies, covering broad areas of Russian scientific, medical, and technical progress for the period 1920-1956.

3. Journals being translated by the Intitute and now available in an English edition. The Institute now publishes a number of selected Russian journals in translation:

Atomnaya Energiya (Atomic Energy)
* Problems of Virology
* Problems of Hematology and Blood Transfusion
* Journal of Microbiology, Epidemiology and Immunobiology
* Biophysics
* Problems of Oncology
* The Sechenov Physiological Journal of the U. S. S. R.
Elektrichestvo (Electricity)
† Physics of Metals and Metallography
† Abstracts of U. S. S. R. Metallurgy
‡ Bulletin of the Academy of Sciences—Geophysical Series
‡ Abstracts of Geophysics—U. S. S. R. Eastern Europe and China
§ Radio Engineering
§ Radio Engineering and Electronics
§ Telecommunications
Applied Mathematics and Mechanics

(* On the initiative and with the financial assistance of the National Institute of Health, United States Department of Health. † With the financial assistance of the National Science Foundation and the Board of Governors of Acta Metallurgica. ‡ With the financial assistance of the National Science Foundation and the American Geophysical Union. § With the financial assistance of the National Science Foundation and in association with the Massachusetts Institute of Technology.)

4. Translation Program of Important Russian Books. The Institute is also assisting with the translation and publication of important Russian books on science, technology, and medicine, and the following titles will soon be available in English, including the work of Academician N. Semenov, who recently shared the Nobel Award for Chemistry with Sir Cyril Hinshelwood, and the classic course of Theoretical Physics by Academician Landau and his colleague, Professor Lifshitz. Academicians Semenov and Landau and Professor Lifshitz are cooperating with the Institute in bringing their books up to date, by adding a great deal of new and hitherto unpublished research results. It is noteworthy that other Soviet authors, whose monographs, books, and articles are being translated by the Institute are also cooperating by bringing their work up to date, checking proofs, making available illustrations, etc. This cooperation is most valuable for the work of the Institute. Among the books being translated are the following:

Ambartsumian	Theoretical Astrophysics
Landau and Lifshitz	Quantum Mechanics Statistical Physics Mechanics of Continuous Media
Shklovsky	The Solar Corona
Fedoseev	Relay Protection of Power Systems
Fock	Theory of Space, Time and Gravitation
Vonsovskii and Shur	Ferromagnetism
Semenov	Some Problems of Chemical Kinetics and Reactivity
Topchiev	Nitration of Hydrocarbons and other Organic Compounds
Topchiev, Zavgorodnii, and Paushkin	Boron-Fluoride and Its Compounds as Catalysts in Organic Chemistry
Krasnosel'skii	Topological Methods in the Theory of Non-Linear Integral Equations
S. G. Mikhlin	Integral Equations and their Applications to Certain Problems in Mechanics, Mathematical Physics and Technology
B. N. Iur'ev	Aerodynamic Survey of Helicopters
V. A. Bodner	Automatics of Aero-Engines
I. A. Zalmanzon and B. A. Cherkasov	Gas Turbine and Ram-Jet Aeroengine Regulation
G. S. Skubachevskii	Gas Turbine Aeroengines
Timakov et al.	Changes in Micro-Organisms
Zdrodovskii et al.	Studies on Rickettsia and Rickettsioses
Churilov et al.	Hemorrhagic Nephronephritis
Petrov et al.	Problems of the Pathogenesis and Immunology of Tumours
Smirnova et al., Ed. Utkin	Theoretical and Practical Problems of Medicine and Biology in Experiments on Monkeys

Institute Services.—Available to learned societies, Government departments, trade associations, individual scientists, doctors, and engineers.

1. Any person in the above categories wishing to keep informed of what is being published in the U. S. S. R. and other countries in the Soviet orbit may apply to the Institute to receive, free of charge, a monthly contents list in English of all the significant articles and books being currently published in his field of interest in these countries. Persons interested in any article mentioned in these contents lists may order from the Institute a full English translation, which will be supplied with a minimum of delay. The charge for such a translation will be on a cooperative cost-sharing basis. This means that the costs will be shared equally with others requesting the article. The costs will be assessed on orders obtained for this translation over a period of six months, and the charges to recipients of these papers will be made six months after the first request.

2. The Institute will undertake to supply, on request, detailed and exhaustive bibliographical information on work published in the U. S. S. R. and other Soviet orbit countries on all subjects in the field of science, technology, and medicine; such services will be quoted for and charged at cost.

3. The Institute with the assistance of its scientific staff will undertake, on request, critical evaluation and selection of any work published in the field of science, technology, and medicine in the U. S. S. R. and other Soviet orbit countries. The Institute will also provide abstracts and résumés of such publications.

4. The Institute will provide, with the cooperation of the respective National Academies of Sciences of the U. S. S. R. and other Soviet orbit countries, to learned Societies, Government departments, and industrial organisations, books, and journals published in the U. S. S. R. and the Soviet orbit countries, including microcards and microfilms when available of books

and articles published over the past twenty years in these countries, including material published during the 1939-1945 war as far as available.

5. The Institute will undertake the additional translation of selected journals and books if suitably recommended by learned societies, Government departments, or trade associations.

6. The Institute can undertake, with the aid of its expert panel of translators, resident all over the world, translation work in all branches of science, technology and medicine from and into any language, including Chinese and Japanese.

7. The Institute will make available to learned societies and individual scientists, doctors, and engineers throughout the world reciprocal services on the same nonprofit basis in return for their cooperation.

Qualified Translators Urgently Needed.—The Institute is urgently in need of qualified scientists, technologists, and doctors with a knowledge of the Russian language who would be able and willing to undertake translation work on a spare-time basis, for which they would be remunerated.

Financial Support and Other Assistance Needed.—Nonprofit foundations, industrial corporations, Government departments, learned societies, and individual scientists desiring to assist in any way with this important program should write to the Administrative Secretary of the Institute, outlining their ideas and suggestions.

Aims and Purpose of the Institute

I. To establish a translation panel of competent and highly qualified translators from Russian and other Slavonic languages into English and to make available the services of the Institute and its translation panel to scientists, learned societies, government agencies, and industry throughout the world on a non-profit-making basis. The Institute shall charge its customers for these services on a cooperative cost-sharing plan.

II. To encourage, coordinate, and foster (by the holding of symposia, for instance) the teaching of Russian at higher seats of learning and to provide the teaching institutions with the necessary textbooks and tools of learning which will enable non-Russian-speaking scientists to acquire quickly a working knowledge of Russian sufficient for them to read Russian scientific literature.

III. To translate and disseminate such of the scientific, technical, and medical literature printed in Russian and other Slavonic languages, which, in the opinion of competent scientific advisors, will be of definite benefit and value to scientists not speaking these languages.

IV. To establish and publish, with the assistance of the appropriate scientific institutions in the U. S. S. R., a series of monographs in the English language reviewing progress in broad areas of Soviet scientific activity.

V. (*a*) To publish a journal devoted to reporting translation work done anywhere in the world from Russian and other Slavonic languages into English in the fields of science, technology, and medicine in order to prevent duplication; (*b*) to serve as a forum in which Soviet and non-Russian-speaking scientists will be able to discuss problems of common concern—both scientific and administrative; (*c*) to be a place where people engaged in the teaching of Russian to non-Russian-speaking scientists can report on their experience and exchange information which will be of assistance to persons working in this field.

VI. To compile and publish specialised dictionaries from and into Russian and the principal Slavonic languages for subjects where such dictionaries are lacking.

VII. To sponsor and foster research into the organisation of scientific information, mechanical systems for storing and retrieving information, and mechanical translation.

VIII. To assist and advise learned societies and professional bodies on their publication problems with a view to reducing the cost of printing and distribution of their publications, in the interests of the wider and more efficient dissemination of scientific information.

Specialists Certified by the American Board of Pediatrics, Inc.—The following pediatricians were certified as specialists in pediatric allergy in New York, April 20, 1958.

Berg, George Shepard, Miami, Fla.
Hillman, Maurice M., New Haven, Conn.
Smelzer, Marilyn Frances, Denver.
Szanton, Victor L., Ansonia, Conn.

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., in Memphis, March 21, 22, and 23, 1958.

Andrea, John, Canton, Ohio.
Arnone, William Henry, Brockton, Mass.
Bernet, Carl P., Jr., Greenwood, Miss.
Boggs, Mauldin J., Abbeville, S. C.
Box, Quellin Thenard, Texas City, Texas.
Briuks, Velta F., Oak Ridge, Tenn.
Brooke, Clement E., Columbia, Mo.
Brown, C. Walter, Alton, Ill.
Browne, Thomas Whittaker, Berkeley, Calif.
Bucheleres, H. Gunther, Chicago.
Burroughs, Lyle Wendell, Tampa, Fla.
Butler, Robert M., Indianapolis.
Chambers, Robert Edward, Gastonia, N. C.
Christu, Chris Nicholas, Moorhead, Minn.
DeGolia, Richard Case, Long Beach, Calif.
Denniston, Joseph Charles, Lewisburg, Ky.
Ehrich, Melvin, Clarksdale, Miss.
Epstein, Eugene U., Memphis.
Flowers, Robert McCreery, Columbus, Ga.
Galusha, Bryant L., Charlotte, N. C.
Hamady, Ruth Brinker, Flint, Mich.
Hanson, Charles Andrew, Geneva, Ill.
Harris, Forest Delbert, Lawton, Okla.
Hartman, Samuel Allen II, Lebanon, Pa.
Hawk, Judson L., Jr., Atlanta.
Hawkins, James Gilson, Pittsburgh.
Heath, Gordon Read, Lakeland, Fla.
Henderson, Patricia Hornbeab, Fresno, Calif.
Hendricks, Edward L., Portland, Ore.
Henry, Frederic C., Toledo, Ohio.
Horowitz, Leon, Tulsa, Okla.
Huntley, Carolyn Coker, Winston-Salem, N. C.
Huxtable, Robert F., Redondo Beach, Calif.
Johnson, Howard H., Jr., Falls Church, Va.
Jones, Barbara, St. Louis.
Kanas, John, Colorado Springs, Colo.
Keppler, Louis L., Jr., Parma, Ohio.
Lonsway, Maurice J., Clayton Mo.
Mathias, Berton J., Flint, Mich.
McCormack, William C., Ames, Iowa.
McEwen, Cecil Ray, Jr., Columbus, Miss.
Meador, Eric B., Jr., Oklahoma City.
Misbach, William D., Sherman Oaks, Calif.
Noble, Andrew, Oakland, Calif.
Nolan, Thomas Campbell, Montgomery, Ala.
Payne, Donald E., Tyler, Texas.
Richardson, Robert Phillips, Detroit.
Ritter, Donald Glenn, Lincoln, Neb.
Robins, Keith I., Dallas, Texas.
Rose, Clifton Page, Downey, Calif.
Roth, Bernard, M., La Mesa, Calif.
Ruben, Herbert Leon, Lexington, Mass.
Sedlis, Emilia, New York.
Shore, Nomie Abraham, Santa Monica, Calif.
Smith, Harris Lake, Memphis.
Smith, Meryleen Bailey, Bluefield, W. Va.
Spaugh, Earle, Charlotte, N. C.
Stafford, Eleanor, Chattanooga, Tenn.
Stanage, Willis Franklin, Yankton, S. D.
Stewart, Marjorie R., Dearborn, Mich.
Stone, James Walter, Lynchburg, Va.
Taylor, William Charles, Utica, N. Y.
Tompkins, Charles Arthur, Chicago.
Tunestam, Nils J., Chicago.
Vance, Minnie Ratliff, Chattanooga, Tenn.
Woodruff, Gerald G., Jr., Anniston, Ala.
Woolley, LeGrand Gardner, Monterey, Calif.
Yeager, John Moore, Alexandria, La.
Young, Gilbert F., Charleston, S. C.

Special Foreign Certificates

Gopalaswami, Digumarthi, Columbus, Ohio.
Kassim, Sami El-Sheikh, Baghdad, Iraq.

Books

BOOK REVIEWS

Aids to the Diagnosis and Treatment of Diseases of Children. By F. M. B. Allen, M.D., F. R. C. P. (Lond.), Nuffield Professor of Child Health, Queen's University, Belfast; Physician, Royal Belfast Hospital for Sick Children, Belfast; Paediatrician, Royal Maternity Hospital, Belfast. Tenth edition. Price, $3.00. Pp. 302. Ballière, Tindall & Cox, 7-8 Henrietta St., Covent Garden, W. C. 2, London, 1957.

This 10th edition pocket-sized volume is one of several English-authored and -published "small textbooks" in which particular emphasis is given to a concise, synoptic presentation of the principles of diagnosis and treatment of pediatric disease.

Dispensing with the usual "textbook preliminaries," the author reviews the care and management of the newborn and neonatal problems, infant feeding, vitamins, and other aspects of nutrition. He then proceeds to present "by system" the diverse affections of children. Treated in separate chapters are the problems of the "infectious fevers," tuberculosis, rheumatic disorders, and syphilis, with appropriate concluding appendiceal sections on diets, useful tables, chemotherapy, and prescriptions.

There are some statements which are at variance with our accepted standards, one example of which is the assertion that prophylactic treatment of the eyes of the newborn is an "unnecessary hospital routine," although this is required by law in the United States. Likewise, in advice regarding umbilical hernia the author states that "straining, coughing and crying predispose to herniation and should be prevented"; yet there is no hint of the manner of such prevention if such a relationship does indeed exist. Admittedly these differences are of probable minor import, but, along with certain unfamiliar words and expressions, they tend to reflect the British accent evident throughout the book.

Implicit throughout is the author's discernment and clear presentation of the requisite principles of diagnosis and treatment. What is undoubtedly the book's chief merit for students and family practitioners, namely, its comprehensive, factual, yet concise nature, might fairly be said to be its chief drawback for the pediatrician, to whom the volume may seem "incomplete."

It should be clear that the book was written as an "aid" and its content was tailored to the needs of the student or family practitioner desirous of a work of this kind. As such, it serves its purpose well.

DEAN J. HEMPEL, M.D.

Child Psychiatry. By Leo Kanner. Price, $8.50. Pp. 777. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave. Springfield, Ill., 1957.

It has now been 10 years since Dr. Kanner has revised his classic textbook on child psychiatry. This present edition has included fewer changes than the revision of 1948 but has brought some newer material into the text. Especially is this true in the description of the very severe emotional disturbances of childhood which fall under the heading of childhood schizophrenia. Dr. Kanner's own interest in this area is represented by his current feelings on the syndrome of autism. In addition, the confusing state of similar clinical pictures is well described, but of current therapeutic approaches only a glimpse is given.

In general, the entire text continues to be more dynamic in its orientation, although in some sections the breakdown of illness by symptom becomes overly elaborate. Viewing the book as the major reference book in this field, it is impressive how quickly certain areas become out of date. This is most noticeable in the fields of newer interest, such as the subject of the psychotic illnesses of childhood. The material on techniques of understanding a child continue to be the most useful parts of the entire book, but the revision will help to maintain its reference value.

HENRY H. WORK, M.D.

Management of the Handicapped Child. Edited by H. Michal-Smith, Ph.D. Price, not given. Pp. 276. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1957.

There are many and varied problems in caring for handicapped children. This book deals

separately with about a dozen different conditions and concludes with a chapter on community aspects and care of the handicapped child. There is a foreword by Dr. Arnold Gesell, who points out that the editor's purpose has been to present an authoritative survey of the most recent developments in the sciences and community services for children needing special assistance. The book does just that, and the authors are outstanding in their special fields. The book contains 276 clearly printed pages, thirteen chapters, references for reading for parents, and in index for easy reference. In addition to discussion of the usually accepted handicaps, there is a chapter on the mentally gifted and chapters on cystic fibrosis and celiac disease and on nephrosis.

This book has been prepared for professional persons, educationalists, physicians, students, social workers, and others who deal with children who are handicapped in one or more ways, and it should be a useful addition to the worker's library.

HADDOW M. KEITH, M.D.

A Synopsis of Children's Diseases. By John Rendle-Short. Price, not given. Pp. 624. John Wright & Sons, Ltd., 42-44 Triangle West, Bristol 8, England, 1957.

"A Synopsis of Children's Diseases" is written in outline form, with emphasis on diagnosis and management, although some space is devoted to the etiology—and even to the history—of certain disorders. The word "synopsis" belies the length and completeness of the book, which makes it more than adequate as a quick reference for the house officer or busy practitioner.

Recent advances in knowledge and therapy are included in this second edition, and there should be little disagreement with Dr. Rendle-Short's factual presentation, although readers on this side of the Atlantic may differ in their approach to well-baby care and treatment of emotional disorders.

While not a substitute for a text, the book is an excellent synopsis—although one hopes that for a third edition the publishers will create a more pleasing format.

Nierenkrankheiten: Physiologie, Pathologie, Klinik und Therapie. By Hans Saare, M.D., Professor of Internal Medicine, Director of University Polyclinic of Internal Medicine at Freiburg I. BR. Price, $14.05. Pp. 540, with 118 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1958.

This book is a splendid review of renal disease written for medical students, practitioners, and those confining their practice to diseases of the kidney. The text is well written and clearly illustrated. It is divided into five sections, each of which is a chapter.

The first chapter is devoted to physiology and anatomy of the kidney. The section on physiology discusses in detail the theories of urine formation, excretion of organic substances, electrolyte metabolism, acid-base equilibrium, water metabolism, hormonal regulations, etc. Keeping abreast of late advances, the author also has included the recent theories concerning the mechanism of urine concentration proposed by Wirz (so-called counter-current-distribution theory).

The second chapter deals mostly with diagnostic methods. Simple urinalyses; determinations of individual constituents of the blood plasma; specific renal-function tests, including clearance methods and their interpretations, as well as radiological diagnosis and renal biopsy, are discussed in detail.

In the last three chapters the clinical aspects of renal diseases and therapy are discussed. Chapter 3 covers the clinical pictures and pathogenesis of certain syndromes such as renal osteopathies and other calcium metabolism disturbances; nephrotic syndrome, and syndromes with partial functional disturbances either due to (1) "proximal tubular insufficiency," e. g., renal diabetes, phosphate diabetes, cystinuria, amino-aciduria, Fanconi syndrome, and Wilson's disease or (2) "distal tubular insufficiency," Lightwood-Albright syndrome, and diabetes insipidus. Extrarenal syndromes, such as are encountered in the state of dehydration and circulatory disturbances, are also discussed. Chapters 4 and 5 provide detailed information as to the etiology, pathology, clinical course, and conventional therapy for those renal diseases coming under the following headings: (1) inflammatory renal diseases (nephritis), (2) degenerative renal diseases (nephrotic syndrome), (3) acute tubular insufficiencies, and (4) vascular renal diseases.

This volume is a welcome addition to the list of books already dealing with this subject and takes its place deservedly among the best of them.

AYSE YUCEOGLU, M.D.

Directory of Pediatric Societies*

INTERNATIONAL

Ninth International Congress of Pediatrics

President: Dr. Allan Ross, P. O. Box 215, Westmount, Montreal 6, Canada.
Secretary-General: Dr. R. L. Denton, P. O. Box 215, Westmount, Montreal 6, Canada.

International Union for Child Welfare

President: Mr. Leonard W. Mayo, 1, rue de Varembé, Geneva, Switzerland.
Deputy President: Judge M. C. de Jong, 1, rue de Varembé, Geneva, Switzerland.
Secretary-General: Mr. D. Q. R. Mulock Houwer, 1, rue de Varembé, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. J. D. Bailey, 140 Brown's Line.
Secretary: Dr. John A. MacLean, 51 Eglinton Ave. East.
Place: Academy of Medicine. Meetings: Once a month.

Asociacion de Pediatrías Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. M. T. Cockburn, 78 Brougham Pl., N. Adelaide.
Vice-President: Mr. K. B. Fraser, Ballow Chambers, Wickham Terrace, Brisbane.
Secretary: Dr. E. B. Sims, 80 Brougham Pl., Adelaide.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Dr. J. Forest Smith, 149 Harley St., London, W. 1.
Secretary: Dr. P. R. Evans, Institute of Child Health, Great Ormond St., London, W. C. 1.

Canadian Paediatric Society

President: Dr. S. C. Weyman, 64 Charlotte St., St. John, N. B.
Secretary: Dr. J. A. P. Turner, 305 Bessborough Dr., Toronto 17.

Clinical Pediatric Society of Israel

Chairman: Dr. I. Heyman, Hadassah Municipal Hospital, Tel Aviv.
Committee: Dr. E. Schoenfeld, Tsahalon Government Hospital, Jaffa, Tel Aviv; Dr. Bernard E. Cohen, Tel Hashomer Government Hospital, Tel Litwinski.
Place: Hospital pediatric service throughout country. Time: Bimonthly.

Danish Pediatric Society

President: Dr. P. W. Braestrup, Bakkedal 24, Hellerup.
Vice-President: Dr. J. Vesterdal, Bülowsvej 18 B, Copenhagen V.
Secretary: Dr. H. Kreutzfeldt, Rosenørnsallé 27, Copenhagen V.
Place: Usually at the University Clinic of Pediatrics, Copenhagen. Time: Monthly.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. E. Lorenz, Mozartgasse 14, Universitäts-Kinderklinik, Graz, Österreich.
Vice-President: Prof. K. Klinke, Moorenstr. 5, Kinderklinik d. med. Akademie.
Secretary: Prof. Dr. J. Jochims, Städt. Krankenhaus Süd, Kronsforder Allee 71/73, Lübeck.
Place: Graz, Austria. Time: Sept. 15-17, 1958.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Finnish Pediatric Association

President: Dr. Niilo Hallman, 11 Stenbäck St., Helsinki.
Vice-President: Dr. Bernhard Landtman, 45 Union St., Helsinki.
Secretary: Dr. Kalle Österlund, Hiihtäjäntie 6 B, Helsinki-Herttoniemi.
Place: Children's Hospital, Helsinki. Time: Every second month.

Greek Pediatric Society

President: Dr. Egle Inglessi, Marrommateon 29, Athens.
Secretary: Dr. Christos Kassimoe, Marni St. 4, Athens.
Place: Athens University. Time: Monthly.

Israel Pediatric Society

Chairman: Prof. S. Rosenbaum, Soutine St. 28, Tel Aviv.
Secretary: Dr. A. Schoenfeld, Dr. Shmargahu Levin St. 6, Tel Aviv.
Place: Jerusalem. Time: Sept. 25-27, 1958.

Nederlandse Vereniging voor Kindergeneeskunde

President: Prof. Dr. W. K. Dicke, Wilhelmina Kinderziekenhuis, Nieuwe Gracht 137, Utrecht.
Honorary Secretary: Dr. H. Reerink, Sophia Kinderziekenhuis, Gordelweg 160, Rotterdam.
Place: Variable. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. E. Eyvind Ek, Oslo City Health Department, Oslo.
Vice-President: Dr. Martin Seip, Pediatric Department, University Hospital, Oslo.
Secretary: K. Harnes, Pediatric Department, University Hospital, Oslo.
Place: Pediatric Department, University Hospital, Oslo. Time: Seven or eight meetings a year.

Paediatric Society of New Zealand

President: Dr. S. L. Ludbrook, Lister Building, Victoria Street East, Auckland C. 1.
Vice-President: Dr. Murray McGeorge, Medical School, Dunedin.
Honorary Secretary: Dr. R. H. Caughey, 58 Symonds St., Auckland C. 1.
Honorary Treasurer: Dr. Alice M. Bush, 18 Symonds St., Auckland C. 1.
Place: Dunedin. Time: August.

Paediatric Society of Victoria

President: Dr. J. F. Williams, 12 Collins St., Melbourne.
Honorary Secretary: Dr. H. E. Williams, Royal Children's Hospital, Carlton.
Place: Lecture Theatre of the Royal Children's Hospital.
Time: Second Wednesday in each month at 8:00 p. m.

Philippine Pediatric Society

President: Dr. Florencio N. Quintos.
Secretary-Treasurer: Dr. Lino. Ed. Lim, Manila.
Place: Physician's Club, Dewey Blvd., Manila. Time: Every two months; last Thursday of September, November, January, and March.

Royal Society of Medicine, Section of Paediatrics

President: Dr. A. Doyne Bell.
Honorary Secretaries: Drs. Trevor P. Mann and H. H. Nixon, 1 Wimpole St., London, W. 1.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month from October to May.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burddorf.

Sociedad Argentina de Pediatría

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviana de Pediatría

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Building. Time: Every Thursday.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Riuz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatría

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatría

President: Dr. Alfonso Vargas Rubiano.
Vice-President: Dr. Darío Gutiérrez Laserna.
Secretary: Dr. Omar García Bustamante.
Treasurer: Dr. Alfonso Gutiérrez Reyes.

Sociedad Cubana de Pediatría (Filial Cienfuegos)

President: Dr. Rafael Viego Delgado.
Secretary: Dr. Ramón Azaret Morón, Santa Cruz No. 167, Cienfuegos, Cuba.
Place: Colegio Médico. Time: 9:00 p. m., Wednesdays, six times a year.

Sociedad Ecuatoriana de Pediatría

President: Dr. Aldo Muggia.
Secretary: Dr. Nicolas Espinosa, Hospital Baca Ortiz, Quito, Ecuador, S. A.
Place: Hospital Baca Ortiz, Quito, Ecuador. Time: Monthly.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínco Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatría del Litoral

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatría y del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Herando Barrios-Angulo.

Sociedad Uruguaya de Pediatría

President: Dr. Julio R. Mareos, Av. 8 de Octubre 2710, Montevideo.
Secretary: Dr. Norma Curbelo Gamba, Enrique Muñoz 932, Montevideo.
Place: Av. Agraciada 1464, piso 13, Montevideo. Time: First and third Wednesdays of each month.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Miguel Raga.
Vice-President: Dr. Jorge Lizarraga.
Secretary: Dr. Herman Mendez C.

Sociedad Yucateca de Pediatría

President: Dr. Humberto Perz Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

SOCIEDADE MENEIRA DE PEDIATRÍA

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

SOCIEDADE DE PEDIATRIA DA BAHIA

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

SOCIEDADE DE PEDIATRIA DE PERNAMBUCO

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

SOCIEDADE DE PEDIATRIA DO RIO GRANDE DO SUL

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

SOCIEDADE PORTUGUESA DE PEDIATRIA

President: Prof. Fonseca e Castro, Praça do Liege 101, Porto.
Vice-President: Prof. Carlos Salazar de Sousa, Avenida da Republica 64, Lisbon.
Secretary: Dr. Mario Cordeiro, Avenida do Restelo 17, Lisbon.
Place: Lisbon. Time: Once a month.

SOCIEDADE DE PUERICULTURA E PEDIATRIA DO MARANBAO

President: Dr. Ordorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

SOCIETA ITALIANA DI PEDIATRIA

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Rémi Archambault.
Vice-President: Dr. Claude Leonard.
Secretary: Dr. Paul Dagenais-Perusse, La Société de Pédiatrie de Montréal, Inc.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Prof. Marcel Lelong, 197 Boulevard St-Germain (VII).
Secretary: Prof. Maurice Lamy, 94 Rue de Varenne (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sevres (XV). Time: 4:00 p. m., third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUEBEC

President: Dr. Antoine Larue, 1193 des Érables, Quebec.
Vice-President: Dr. Antoine Bélanger, 31 Guénette, Lévis.
Secretary: Dr. Maurice Richard, 1215 des Pins, Sillery.
Place: Quebec City. Time: First week of May and November.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. H. L. Wallace, Durban.
Honorary Secretary-Treasurer: Dr. F. Walt, 126 Trust Building, Gardiner St., Durban.

SWEDISH PEDIATRIC SOCIETY

President: Prof. Bo Vahlquist, Pediatriska Kliniken, Akademiska Sjukhuset, Uppsala.
Secretary: Dr. Marcel d'Avignon, Barnkliniken, Karolinska Sjukhuset, Stockholm.
Place: Svenska Läkaresällskapet, Stockholm. Time: Second Friday of every month, except summer.

UNITED STATES

National

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Stewart H. Clifford, 1101 Beacon St., Brookline 46, Mass.
Vice-President: Dr. James C. Overall, 1924 Church St., Nashville 3, Tenn.
Executive Secretary: Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.
Place: Palmer House, Chicago. Time: Oct. 20-23, 1958.

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. George M. Wheatly, 1 Madison Ave., New York.
Vice-Chairman: Dr. Harry F. Dietrich, 133 S. Lasky Dr., Beverly Hills, Calif.
Secretary: Dr. Wyman C. C. Cole Sr., 1063 Fisher Building, Detroit.

AMERICAN PEDIATRIC SOCIETY

President: Dr. A. Ashley Weech, Children's Hospital, Cincinnati 29.
Vice-President: Dr. Alton Goldbloom, 307 Medical Arts Building, Montreal, Canada.
Secretary: Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washington 8, D. C.
Place: The Inn, Buck Hill Falls, Pa. Time: May 6-8, 1959.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Edward L. Pratt, Southwestern Medical School, Dallas, Texas.
Vice-President: Dr. Alexander Nadas, 300 Longwood Ave., Boston 15.
Secretary: Dr. Sydney S. Gellis, 818 Harrison Ave., Boston 18.

Sectional

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. R. H. Wakefield, 410 N. University Ave., Provo, Utah.
Vice-President: Dr. Wesley H. Anderson, 39 Virginia Professional Building, Ogden, Utah.
Secretary: Dr. Thales H. Smith, 220 N. University Ave., Provo, Utah.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Alice Whittier, 143 Neal St., Portland 4, Maine.
Vice-President: Dr. Sidney Gellis, Boston City Hospital, Boston.
Secretary: Dr. Harry Shwachman, Children's Hospital, Boston.
Place: Three meetings in Boston; spring meeting, variable. Time: Four meetings per year.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. Gorham Babson, 1107 S. W. 13th, Portland 5, Ore.
President-Elect: Dr. Norman Murphy, Seattle.
Secretary: Dr. Peter Spohn, 3195 Granville St., Vancouver, B. C.
Meeting: April, Seattle.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. C. O. Kohlbry, 226 N. 1st Ave., Duluth, Minn.
Vice-President: Dr. John D. Bailey, Box 849, Rapid City, S. D.
Secretary-Treasurer: Dr. John J. Galligan, 868 Lowry Medical Arts, St. Paul.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Ward L. Chadwick, 1809 E. 18th Ave., Denver.
Vice-President: Dr. Kenneth W. Dumars Jr., 112 E. St. Vrain, Colorado Springs, Colo.
Secretary, Dr. Frank J. Cozzetto, 2401 E. 6th Ave., Denver 6.
Place: Writer's Manor. Time: Six times a year.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Gordon L. Richardson, 10711 Riverside Dr., North Hollywood, Calif.
Vice-President: Dr. John Wilcox, 150 Nemha St., Pomona, Calif.
Secretary: Dr. Robert Shirley, 11633 San Vincente Blvd., Los Angeles 49.
Time: Four closed meetings a year; one open lecture series, usually in March.

WESTERN SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. James F. Bosma, 1940 So. 2d East, Salt Lake City.
Vice-President: Dr. William Deamer, Dept. of Pediatrics, University of California, San Francisco.
Secretary: Dr. Robert H. Alway, Stanford School of Medicine, San Francisco.
Place: Salt Lake City.

State

ACADEMY OF PEDIATRICS, INDIANA CHAPTER

President: Dr. William M. Browning, 3740 Central Ave., Indianapolis 5.

ALABAMA PEDIATRIC SOCIETY

President: Dr. Thomas C. Nolan, 803 Adams Ave., Montgomery 5.
Vice-President: Dr. Jerome A. Weaver, 5381 1st Ave. N., Birmingham.
Secretary: Dr. Paul S. Foster, 131 S. Union St., Montgomery 4.

ARIZONA STATE PEDIATRIC SOCIETY

President: Dr. B. P. Starts, 1018 N. Country Club Rd., Tucson.
Secretary: Dr. Jack H. Demlow, 130 S. Scott, Tuscon.
Time: Spring and fall.

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.
Secretary: Dr. Percy H. Jennings Jr., 1650 Walnut St., Berkeley 9.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Henry Morton, 1950 Arlington St., Sarasota.
Vice-President: Dr. Burns A. Dobbins, 120 E. Broward Blvd., Fort Lauderdale.
Secretary: Dr. Harry M. Edwards, 113 E. Broadway, Ocala.
Time: Spring and fall.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Stephan C. Redd, Atlanta.
Vice-President: Dr. Milton Mazo, Savannah.
Secretary-Treasurer: Dr. C. Dixon Fowler, 27 8th St., N. E., Atlanta 9.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Charles S. Culotta, 291 Whitney Ave., New Haven.
Secretary: Dr. Winston C. Hainsworth, 132 Mansfield Ave., Willimantic.
Place: Variable. Time: Three meetings a year, fall, winter, spring.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. A. R. Eveloff, 1025 S. 7th St., Springfield.
Secretary: Dr. Lawrence Breslow, 2424 W. Peterson, Chicago 45.
Place: Chicago. Time: May, at time of state meeting.

IOWA PEDIATRIC SOCIETY

President: Dr. Maryelda Rockwell, 220 Tucker Bldg., Clinton.
Vice-President: Dr. Harold E. Farnsworth, 612½ Lake Ave., Storm Lake.
Secretary: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines 11.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting; fall meeting in September at University Hospital, Iowa City.

KANSAS STATE PEDIATRIC SOCIETY

President: Dr. T. E. Young, 103½ E. 9th St., Winfield.
Vice-President: Dr. Holbert P. Jubelt, 1200 Fremont St., Manhattan.
Secretary: Dr. Thomas C. Hurst, 405 K. F. H. Building, Wichita.
Place: Emporia. Time: 9:30 a. m., first Saturday after Labor Day.

KENTUCKY PEDIATRIC SOCIETY

President: Dr. Owen S. Ogden, Louisville.
Vice-President: Dr. Robert McLeod, Somerset.
Secretary: Dr. Kenneth Crawford, Louisville.

LOUISANA STATE PEDIATRIC SOCIETY

President: Dr. Conway Magee, Lake Charles.
Vice-President: Dr. Bertha Wexler, New Orleans.
Secretary: Dr. Dorothy York, 2902 Napoleon Ave., New Orleans.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

President: Dr. Harry A. Towsley, University Hospital, 1313 Ann St., Ann Arbor.
Secretary: Dr. Charles Frank Payton, 611 S. Washington, Royal Oak.

Montana Pediatric Society

President: Dr. John Halseth, Great Falls.
Secretary: Dr. George Barmeyer, Missoula.
Time: Midwinter and fall.

Nebraska Pediatric Society

President: Dr. E. S. Wegner, 724 Sharp Bldg., Lincoln.
Vice-President: Dr. Robert Grant, 909 Sharp Bldg., Lincoln.
Secretary: Dr. Gilbert Schreiner, 125 N. 38th St., Omaha.
Place: Omaha. Time: Third Thursday of each month at the Children's Memorial Hospital, Omaha.

New Hampshire Pediatric Society

President: Dr. Robert F. Wilson, 113 Locust St., Dover.
Secretary: Dr. Arthur Laidlaw, Keene Clinic, Keene.
Place: Concord, Laconia, Dover, Hanover. Time: Four times a year.

New Mexico Pediatric Society

President: Dr. Albert S. Lathrop, P. O. Box 912, Coronado Bldg., Santa Fe.
Vice-President: Dr. Guy E. Rader, 4120 Silver S. E., Albuquerque.
Secretary: Dr. Carol K. Smith, P. O. Box 2056, Coronado Bldg., Santa Fe.
Place: Variable. Time: Four times a year.

North Carolina Pediatric Society

President: Dr. Leroy J. Butler, Winston-Salem.
President-Elect: Dr. Thomas A. Hensen, Greensboro.
Secretary-Treasurer: Dr. John F. Lynch Jr., Greensboro.

South Carolina Pediatric Society

President: Dr. Fred Adams, 157 Pine St., Spartanburg.
Vice-President: Dr. C. Guy Castle Jr., 1417 Gregg St., Columbia.
Secretary: Dr. Charles Zemp, 1105 Lyttleton St., Camden.
Place: Columbia and Myrtle Beach. Time: September and May of each year.

Tennessee State Pediatric Society

President: Dr. Stewart Smith, 605 Lindsay St., Chattanooga.
Vice-President: Dr. J. R. Bowman, W. Fairview at Boone, Johnson City.
Secretary: Dr. Robert G. Jordan Jr., Le Bonheur Children's Hospital, Memphis.

Texas Pediatric Society

President: Dr. Thomas McElhenney, 1402 Nueces St., Austin.
Secretary: Dr. James N. Walker, 5216 W. Freeway, Fort Worth.
Place: Fort Worth. Time: Oct. 17-18, 1958.

Virginia Pediatric Society

President: Dr. Harry Cox, 113 Fauquier St., Portsmouth.
Vice-President: Dr. Robert H. Cox Jr., Allied Arts Building, Lynchburg.
Secretary: Dr. O. Watts Booth, 87 29th St., Newport News.

Wisconsin State Medical Society, Section of Pediatrics

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave. (12).
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave. (6).
Place: Allen Memorial Medical Library. Time 8:15 p. m., October, December, February, and March.

Akron Pediatric Society

President: Dr. Albert I. Reaven, 1661 W. Market St.
Vice-Pres.: Dr. Edward A. Lawan, 111 W. State St.
Secretary: Dr. Francis J. Waickman, 1602 Portage Trail, Cuyahoga Falls, Ohio.
Time: Quarterly.

Baltimore City Medical Society, Pediatric Section

President: Dr. Melchijah Spragins, 102 Alleghany Ave., Towson 4, Md.
Vice-President: Dr. Harry H. Gordon, Sinai Hospital of Baltimore, Inc., Monument St. and Rutland Ave. (5).
Secretary: Dr. B. M. Debuskey, 2501 W. Belvedere Ave.
Place: 1211 Cathedral St. Time: Second Tuesday in November, January, and March at 8:30 p. m.

Baton Rouge Pediatric Society

President: Dr. Clifton Morris, Roumain Building.
Vice-President: Dr. John Ray Powers, 3347 Government St.
Secretary: Dr. Stephen Madey, 1401 N. Foster.
Time: Quarterly as called.

Bronx Pediatric Society

President: Dr. Jess Diamond, 1900 Grand Concourse (57).
Vice-President: Dr. Archie Cohn, 2280 Grand Ave.
Secretary: Dr. Arthur A. Goldfarb, 1150 Grand Concourse.
Place: Morrisania Hospital. Time: Second Wednesday of each month.

Brooklyn Academy of Pediatrics

President: Dr. Adolph Emerson, 7721 Ridge Blvd. (9).
Vice-President: Dr. Joseph Pincus, 881 Washington Ave. (25).
Secretary: Dr. Morris Steiner, 456 E. 19th St. (26).
Place: Granada Hotel. Time: Fourth Wednesday of each month.

Buffalo Pediatric Society

President: Dr. Norman C. Bender, 227 Colvin Ave.
Vice-President: Dr. Thomas S. Bumbalo, 354 Lincoln Parkway.
Secretary: Dr. Lois J. Plummer, 131 Linwood Ave.
Place: Alternating Buffalo Children's Hospital and Edward J. Meyer Memorial Hospital.
Time: Fall, winter, and spring and on call.

Central Illinois Pediatric Society

President: Dr. Howard R. Miller, Peoria.
President-Elect: Dr. Paul P. Pierce, 1900 Brown St., Alton.
Secretary-Treasurer: Dr. Richard E. Dukes, 602 W. University Ave., Urbana.
Place: Variable. Time: Fall and spring.

Central New York Pediatric Club

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester
Vice-President: Dr. Howard A. Gilmartin, Schenectady.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester 7.
Place: Variable. Time: Spring and fall.

Central Ohio Pediatric Society

President: Dr. Samuel Edelman, 327 E. State St., Columbus.
Secretary: Dr. James Scheip, 375 E. Town St., Columbus.
Place: Variable. Time: Fourth Wednesday of each month.

Chicago Pediatric Society

President: Dr. Ralph H. Kunstadter, 57 Bellevue St.
Vice-President: Dr. Noel G. Shaw, 2901 W. Central St., Evanston, Ill.
Secretary: Dr. Raymond R. Grissom, 715 Lake St., Oak Park, Ill.
Place: Children's Memorial Hospital. Time: 8 p. m., third Tuesday in each month.

Cincinnati Pediatric Society

President: Dr. Daniel V. Jones, 7373 Brookcrest Dr.
Vice-President: Dr. Harold A. Cassady, 2728 Erie Ave.
Secretary: Dr. Carl V. Ochs, 2727 Madison Rd.
Place: Children's Hospital. Time: Quarterly.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Norman C. Woody, 515 Elizabeth St.
Vice-President: Dr. Joseph Oshman, 1010 Ohio.
Secretary: Dr. Mary McCaskey, Medical Arts Building.
Time: Fourth Wednesday, every two months.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave.
Place: Children's Hospital of Texas. Time: 6:30 p. m., first Thursday in each month.

Des Moines Pediatric Society

President: Dr. Charles L. Burr, 5701 Hickman Ave.
Vice-President: Dr. James E. Dyson, 3200 University Ave.
Secretary-Treasurer: Dr. Glen E. Nielsen, 3009 Ingersoll Ave.
Place: Des Moines Golf and Country Club. Time: Fourth Tuesday of each month.

Detroit Pediatric Society

President: Dr. Louis E. Heideman, 20211 Greenfield (35).
Vice-President: Dr. Charles G. Jennings, 14827 E. Jefferson (15).
Secretary: Dr. Douglas L. Wake, 1307 S. Washington, Royal Oak, Mich.
Place: Veterans Memorial Building. Time: Wednesdays, five times a year.

Fort Worth Pediatric Society

President: Dr. Harry Womack, 1424 W. Peter Smith.
Secretary: Dr. Blanche O. Terrell, 1425 Pennsylvania Ave.
Place: Variable. Time: Fourth Friday of each month.

Hinterland Pediatric Society

President: Dr. John Wilcox, 150 Nemaha St., Pomona, Calif.
Vice-President: Dr. Edward Zeman, 3616 Main St., Riverside, Calif.
Secretary: Dr. George A. Chalfant, 1086 San Bernardion Rd., Upland, Calif.
Place: Alternating San Bernardino, Riverside, and Pomona. Time: Fourth Tuesday of February, May, Sebtember, and November.

Honolulu Pediatric Society

President: Dr. Clifford K. Kobayashi, 1423 Kalakaua.
Secretary-Treasurer: Dr. Donald I. B. Char, Children's Hospital.
Recording Secretary: Dr. Robert G. Dimler, 539 Kailna Rd., Lanikai, Oahu.
Place: Members' homes. Time: 6:30 p. m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Robert A. Gardner, 4006 Montrose.
Vice-President: Dr. Helen G. Schaffer, 2905 La Branch.
Secretary: Dr. Robert H. Hardie, 1701 S. Shepherd Dr.
Place: Doctor's Club. Time: Fourth Tuesday every other month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Houge, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

LONG BEACH PEDIATRIC SOCIETY

President: Dr. Selby V. Love, 108 Cannons Lane (6).
Vice-President: Dr. Milton Katz, 1868 Pacific Ave.
Secretary: Dr. David M. Rozran, 911 E. San Antonio Dr.
Place: University Club, 1150 E. Ocean Blvd. Time: First Tuesday of each month.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Margaret H. Jones, 405 Hilgard Ave. (24).
Vice-President: Dr. Wendell M. Redfern, 720 N. Brand Blvd., Glendale (3).
Secretary-Treasurer: Dr. Morris J. Naiditch, 239 S. La Cienega Blvd., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Building. Time: Second Thursday in September, November, January, March, and May.

LOUISVILLE PEDIATRIC SOCIETY

President: Dr. Shelby V. Love, 108 Cannons Lane (6).
Vice-President: Dr. Edwin Paul Scott, 3610 Lexington Rd.
Secretary: Dr. Paul Patrick Hess, Floyd Company Bank Building, New Albany, Ind.
Place: Variable. Time: Four times a year.

MEDICAL SOCIETY OF THE COUNTY OF KINGS, BROOKLYN, PEDIATRIC SECTION

President: Dr. Arthur L. Ruby.
Vice-President: Dr. David Dragutsky.
Secretary: Dr. Abraham Gilner, 303 Beverly Rd. Brooklyn 18.
Treasurer: Dr. Saul Starr.

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Secretary: Dr. John E. Cassidy, 9911 Old Georgetown Rd., Bethesda, Md.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. M. Blake Arnoult, 670 Waring Rd.
Vice-President: Dr. Kinsey M. Buck, 1193 Madison Ave.
Secretary: Dr. William W. Mason, 3314 Poplar Ave.
Place: Le Bonheur Hospital. Time: Second Tuesday of each month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. Helen Zillmer, 425 E. Wisconsin Ave.
Vice-President: Dr. Sam Rosenberg, 2303 N. 49th St.
Secretary: Dr. Ted Buszkiewicz, 3333 S. 27th St.
Place: University Club. Time: Second Wednesday of alternate months.

MOBILE PEDIATRIC SOCIETY

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile.
Place: Admiral Semmes Hotel. Time: 7:30 p. m., fourth Thursday of September, November, January, March, and May.

MONTGOMERY COUNTY PEDIATRIC SOCIETY

President: Dr. Harris P. Dawson, 45 Adams Ave., Montgomery, Ala.
Vice-President: Dr. William R. Britton, 133 S. Union, Montgomery.
Secretary-Treasurer: Dr. Thomas C. Nolan, 803 Adams Ave., Montgomery.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. Harry M. Estes, 1924 Hayes St.
Secretary: Dr. Ray L. Dubuisson, Formosa Building, Hillsboro Dr.
Place: Members' homes. Time: Third Thursday of each month.

NASSAU PEDIATRIC SOCIETY

President: Dr. Virginia Lent, 285 N. Franklin St., Hempstead, N. Y.
Vice-President: Dr. Selma Buchbinder, 295 Harvard Ave., Rockville Centre, N. Y.
Secretary-Treasurer: Dr. David Posner, 98 Wolcott Rd., Levittown, N. Y.
Time: Second Monday in February, April, June, October, and December.

New Orleans Pediatric Society

President: Dr. J. L. Treadway, 4325 Clara St.
Vice-President: Dr. Norman Robinson, 1505 Louisana Ave.
Secretary: Dr. Thomas Furlowe, 2110 Foy.
Place: Variable. Time: Quarterly.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Benjamin Kramer, 60 Plaza St., Brooklyn.
Secretary: Dr. Henry L. Barnett, 535 East 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St., New York
Time: 8:30 p. m., every second Thursday of October through May.

Northern California Pediatric Society

President: Dr. Samuel Hurwitz, 6200 Geary Blvd., San Francisco 21.
Vice-President: Dr. Percy Jennings Jr., 1650 Walnut St., Berkeley 9.
Secretary: Dr. Agnes G. Plate, 2445 Ocean Ave., San Francisco 27.
Place: Variable. Time: Every three months.

Northern Ohio Pediatric Society

President: Dr. William Champion, 2323 Prospect Ave., Cleveland.
Secretary: Dr. Grafton C. Fanney Jr., 26151 Euclid Ave., Euclid.
Time: Four times a year.

Oklahoma City Pediatric Society

President: Dr. Charles L. Freed, 430 N. W. 12th St.
Secretary: Dr. Jerome D. Shaffer, 1200 North Walker.
Place: Variable. Time: On call.

Philadelphia Pediatric Society

President: Dr. Hubert A. Rayster Jr., 888 Glenbrook Ave., Bryn Mawr, Pa.
Vice-President: Dr. Rachel Ash, 257 S. 16th St.
Secretary: Dr. Robert H. High, 400 Kent Rd., Cynwyd, Pa.
Place: College of Physicians. Time: Second Tuesday of each month, October to May.

Pittsburgh Pediatric Society

President: Dr. Robert Macdonald, 448 Brownsville Rd.
Vice-President: Dr. Bernard I. Michaels, 3500 5th Ave. (13).
Secretary: Dr. James Reilly, 2331 Laketon Rd. (35).
Place: Variable. Time: January, March, May, September, November.

Queens Pediatric Society

President: Dr. Ben Goldsmith, 4027 Murray St., Flushing 54, N. Y.
Vice-President: Dr. Fred Castrovinci, 3357 75th St., Jackson Heights 72, N. Y.
Secretary: Dr. Emanuel Fletcher, 14010 Franklin Ave., Flushing 55, N. Y.
Place: Seminole Club. Time: Second Tuesday of February, April, October, and December.

Richmond Pediatric Society

President: Dr. Helen L. Morton, 5011 Forest Hill Ave.
Vice-President: Dr. Thomas S. Chalkley, 3011 Monument Ave.
Secretary: Dr. Lillian C. Lindemann, 4708 Cary St. Rd.
Place: Richmond Memorial Hospital. Time: Third Thursday of the month, September through May.

St. Louis Pediatric Society

President: Dr. Alfred S. Schwartz.
Vice-President: Dr. James P. King.
Secretary: Dr. Mirriam H. M. Pennoyer, 500 Kingshighway Blvd.
Place: Medart's Restaurant. Time: 7:00 p. m., second Thursday of each month from September to May, inclusive.

San Antonio Pediatric Society

President: Dr. B. B. Shaver, Medical Professional Building.
Vice-President: Dr. J. Newton, 302 Craydon.
Secretary: Dr. Scott Stewart, 123 Ogden Lane.
Place: Santa Rosa Hospital. Time: Second Wednesday of each month.

Santa Barbara Pediatric Society

President: Dr. Louis Needles, County Health Department.
Secretary: Dr. Newton Wayland, 1515 State St.
Place: Variable. Time: On call.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p. m., fourth Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Bruce D. Graham, University Hospital, Department of Pediatrics, Ann Arbor.
Secretary: Dr. George H. Lowrey, University Hospital, Department of Pediatrics, Ann Arbor.
Place: University Hospital, Ann Arbor. Time: May.

Waco Pediatric Society

President: Dr. A. O. Manske, 1917 Austin Ave.
Secretary: Dr. J. M. Garrett, 1410 Austin Ave.
Place: 2524 Austin Ave. Time: Last Tuesday of each month.

Westchester County Academy of Medicine, Pediatric Section

President: Dr. Edward A. Hardy, 145 Corlies Ave., Pelham, N. Y.
Secretary: Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Place: Westchester County Medical Society, Purchase, N. Y.
Time: Quarterly.

Western Michigan Pediatrics Society

President: Dr. John W. Thompson, 833 Lake Drive, S. E., Grand Rapids.
Vice-President: Dr. Ethon L. Stone, 721 17th St., Jackson.
Secretary: Dr. Donald C. Johns, 655 Broadview S. E., Grand Rapids.
Place: Grand Rapids in November and March. Other west Michigan cities in September and June.

Wichita Pediatric Society

President: Dr. Wm. F. McGuire.
Secretary: Dr. Katherine Pennington, Sedgwick County Medical Society, Schwiter Building, Wichita, Kan.
Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.

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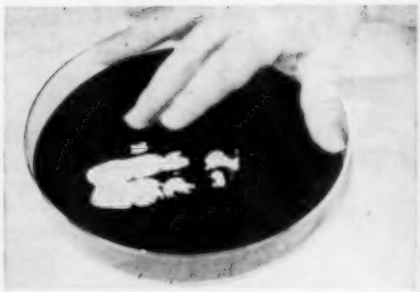

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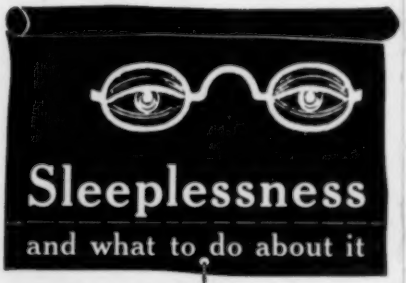

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*Ratner, Bret, Crawford, L. V.; and Flynn, J. C.: Amer. J. Dis. Child., 91:593, 1956

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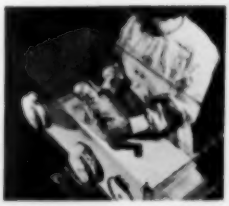

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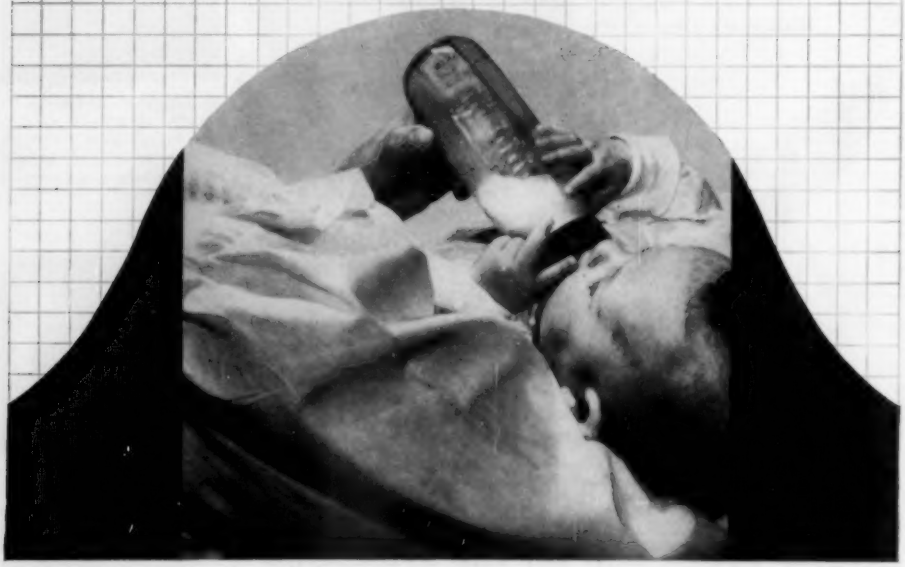

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(1) Hansen, A. E., et al.: Fed. Proc. *16:* 387, 1957.
(2) Hansen, A. E.: Pediat. *21:* 494, 1958.

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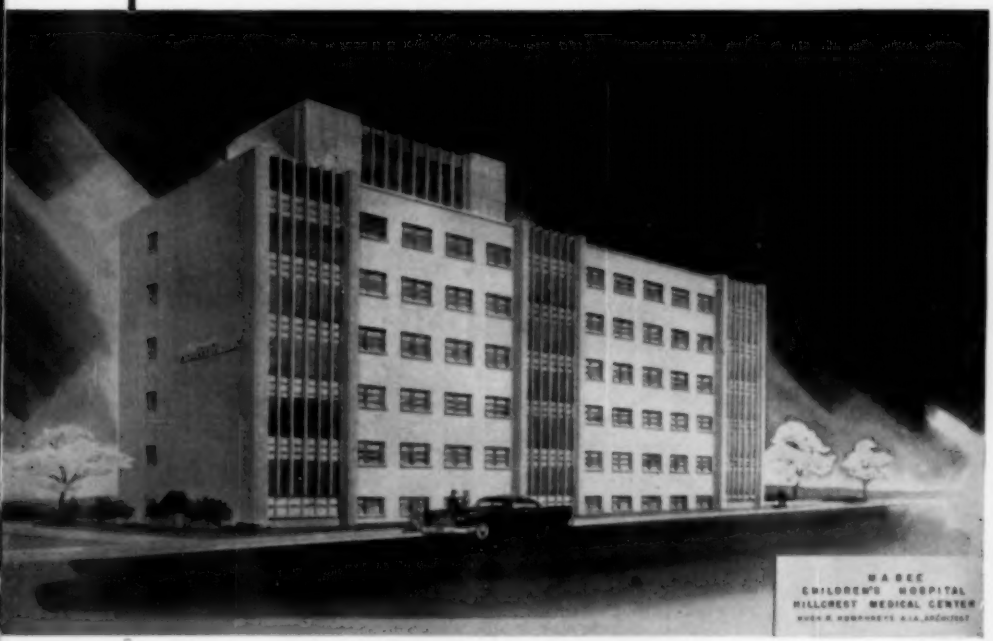

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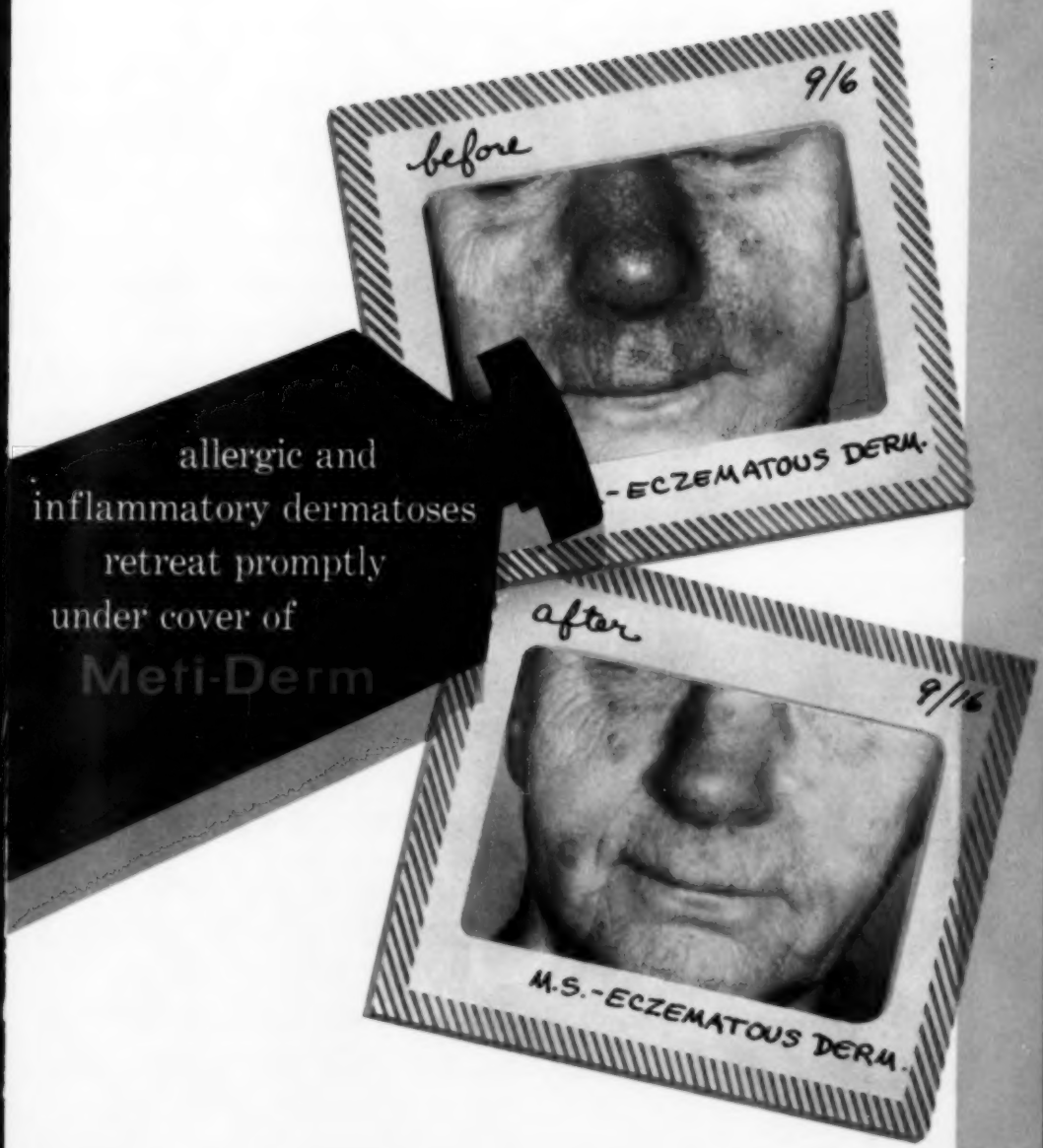

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1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., *et al.*: J.A.M.A. *161*:515 (June) 1956. 3. Hoekenga, M. T.: World M. J. *3*:299 (Sept.) 1956.

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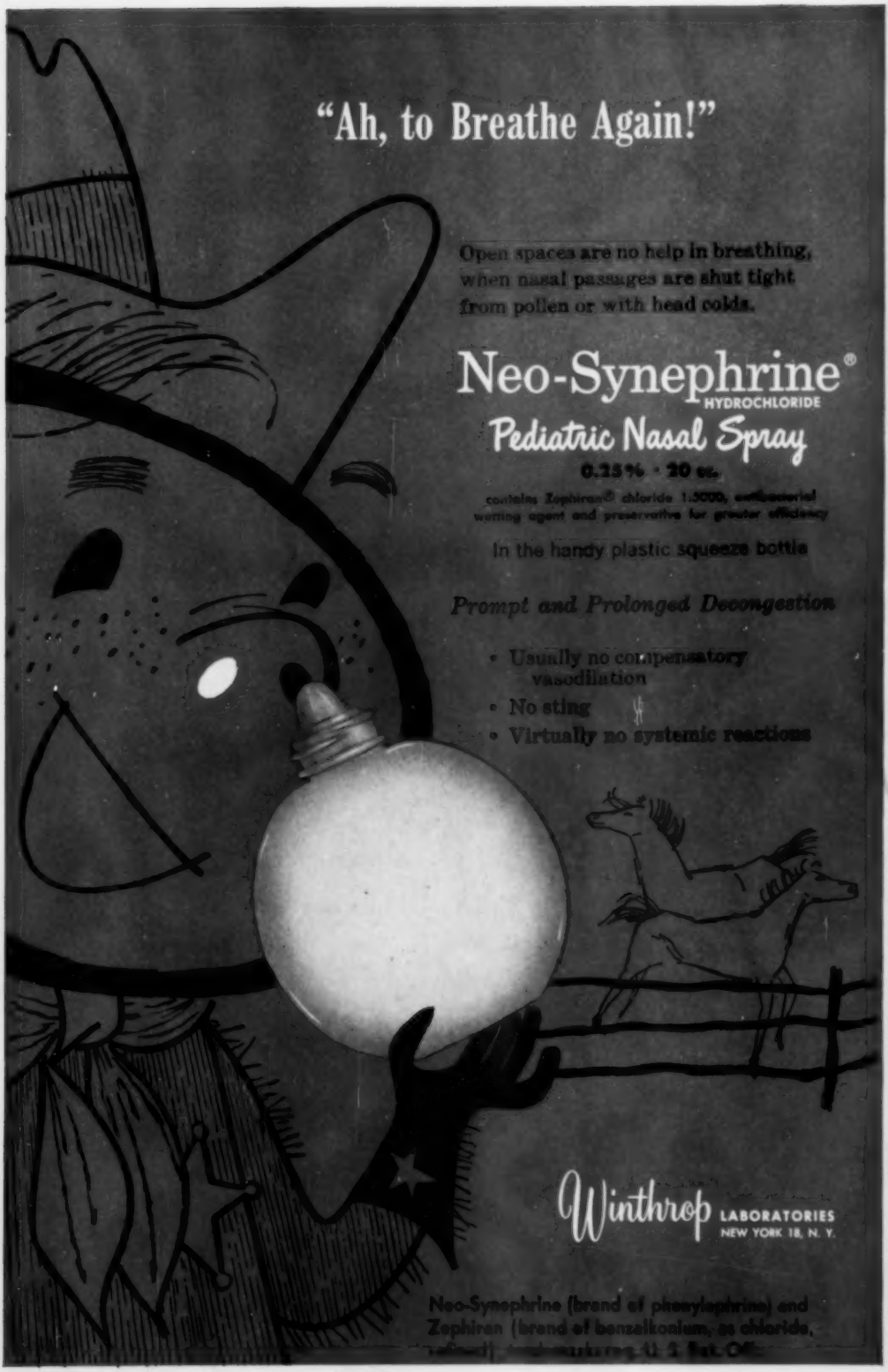
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Neo-Synephrine (brand of phenylephrine) and Zephiran (brand of benzalkonium, as chloride,